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QUINOLINEMETHANOL ANTIMALARIALS.(U)
DEC 74 R E LUTZ, A BURGER DA-49-193-MD-2955

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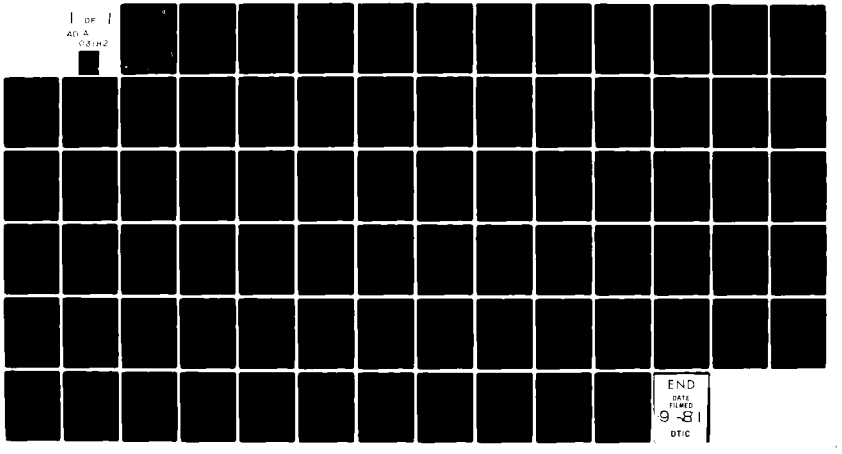

LEVEL II

AD

QUINOLINEMETHANOL ANTIMALARIALS

FINAL REPORT

by

ROBERT E. LUTZ, Alfred Burger
Professor of Organic Chemistry (Emeritas, 1970)
Principal Investigator

December 1974

For the 4-year and 5-month Extension, 5 May 1966 to October 1970

Including work directed by

ALFRED BURGER
Professor of Organic Chemistry
Co-Principal Investigator for the First Year, 5 May 1966 to 4 May 1967

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Office of the Surgeon General, Washington, D.C. 20315

Contract No. DA-49-193-MD-2955

University of Virginia
Department of Chemistry, Charlottesville, Virginia 22901

I. Personnel

Principal Investigator, 1966-present, Robert E. Lutz, (Ph.D., Harvard), Professor of Chemistry, University of Virginia, Emeritas, 1970. (Principal Investigator during World War II at U.Va. on Synthesis of Antimalarials under a contract, recommended by the Committee on Medical Research, under the Office of Scientific Research and Development).

Co-Principal Investigator, 1966 only, Alfred Burger, (Ph.D., Vienna), Professor of Organic Chemistry, University of Virginia.

Postdoctoral Research Associates

1966-7	David W. Boykin, Jr. (Ph.D., U. Ala.) Professor, Georgia State University.
1966-9	A. R. Patel (Ph.D., California)
1966-7	S. N. Sawhney (Ph.D., Hull)
1966-7	Roger M. Pinder (Ph.D., Hull)
1967-8	David P. Clifford (Ph.D., East Anglica)
1969-70	Cyrus J. Ohnmacht (Ph.D., Lehigh Univ.)
1968-9	H. Randall Munson (Ph.D., Georgetown)
1969-70	James M. Sanders (Ph.D., Rice)(supported in smaller part by a National Science Foundation grant to REL)

Postgraduate Research Assistants

1967-8	Richard E. Johnson (B.S., Kent)
1967-8	Charles R. Wetzel (M.S., U.Va., 1968)
1968-9	Freddy Davis (B.S., Pikeville)(M.S., U.Va. 1969)
1968-70	James R. Shanklin (B.S., U.Va.)(Ph.D., U.Va., 1971) (supported in considerable part by NASA traineeship 1968-9 and A.H. Robins Co. research grant to REL)

II. Foreword and Introduction

This project began 5 May 1966 as part of the U.S. Army Program of Synthesis of Antimalarials to meet needs for drugs effective against new resistant strains of P. falciparum. For the first year it was under co-principal investigators, Robert E. Lutz and Alfred Burger; and it was continued under REL for another three years (to his retirement, summer 1970). The Chemistry Department then closed laboratory facilities for further work on unfinished last-minute problems. This Final Report was delayed in favor of attempts to complete the work elsewhere, and by decision of REL first to write the last five of the total of eleven papers which describe the results and which are incorporated herein. Papers 7-9 have since been published (1971, 1973); and it is expected that papers 10 and 11 will be published during 1975. Grateful Acknowledgment is made of the intelligence, perseverence, initiatives and hard work of the above named Postdoctoral and Postgraduate Research Associates and Assistants.

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III. Table of Contents

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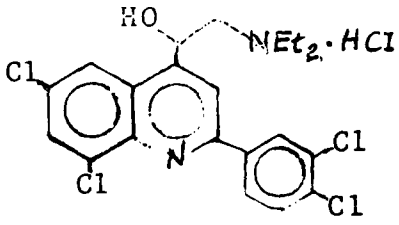
IV. Summary of Results

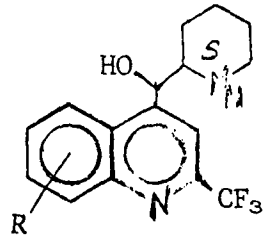
Seventy seven new aminoalcohols, chiefly of the 4-quinoline type, were synthesized, following older leads and in exploration of new ones (List, p. 70). The hope was to eliminate the phototoxicity then supposed to be assiciated with nuclear through-conjugation of the 2-arylquinoline ring system However, the highly curative compound 1 made during World War II by the Virginia group, despite its phototoxicity in animals, was chosen by WRAIR for clinical study in man where it proved highly successful both as prophylactic and cure for several strains of P falciparum, with phototoxicity inconsequential.

Part 1. Nineteen new 2-aryl-4-quinoline aminoalcohols, analogs of 1, proved highly active and curative against P berghei, but they were phototoxic in animals. Attempted synthesis of 2-pentafluoro analogs was not completed (p. 16). Five new analogs without the 2-aryl were ineffective (p 6).



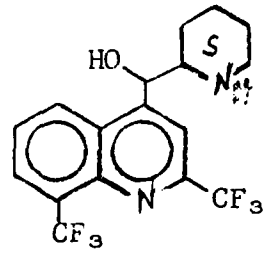
1

Highly curative in animals and man; phototoxic in animals but not in man.



2

Moderately active; phototoxic in animals.



3

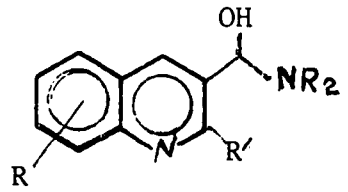
Highly curative and non-phototoxic, both in animals and man

Part 2. Ten derivatives in which the 2-aryl was replaced by 2-CF_3 (2), showed moderate antimalarial activities but were phototoxic in animals (p 17). Four bis-CF_3 analogs (of 3) were highly curative of P. berghei and non-phototoxic in animals; and clinical trials of the 2,8-bis-CF_3 compound 3 in man have proved highly successful (p. 20).

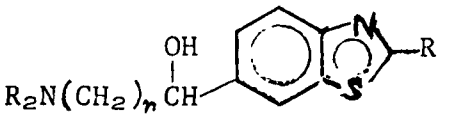
Part 3. Shifting the aminoalcohol chain from quinoline position-4 to 3 was ineffective in eight compounds (4) without a 2-aryl group (and also in six 2-aryl analogs made by the Monsanto Research Corp. group under P F. Donovan and W. R. Smith) (p.23).

Part 4. Twelve quinoline isosteres, 6-benzothiazole aminoalcohols 5, proved ineffective against P berghei in mice (p 30).

-4-

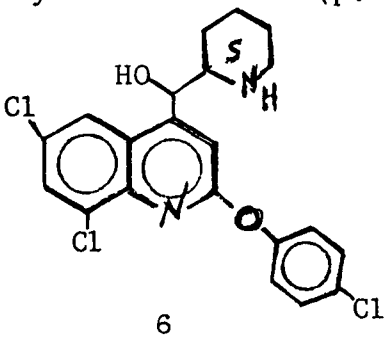


4
Inactive

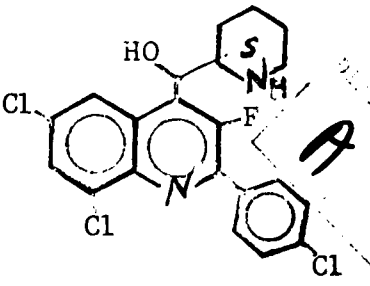


5
Inactive

Part 5. Twelve 4-quinoline aminoalcohols carrying 2-p-substituted-phenoxy (analogs of 6) were made, and also 2-(N-p-chloro-anilino) analogs, hoping that interruption of the 2-phenylquinoline conjugation by the heteroelement and conversion to a forked conjugated system would eliminate phototoxicity without impairment of antimalarial activity. However, the five that were tested were phototoxic. The very high curativity of the 6,8-dichloro-2-(p-chlorophenoxy) compound (6) was comparable with that of 1, with high probability that (as with 1) the animal phototoxicity would not carry over into man (p. 33).



6
Highly curative;
phototoxic in animals



7
Highly curative;
phototoxic in animals

Part 6. Four 2-aryl-quinoline aminoalcohols carrying Cl, Br, F, or O-Me in the 3-position were synthesised in the hope that steric interference with the nuclear planarity and through conjugation would lower phototoxicity without detriment to antimalarial curativity. Three of these with favorable 6,8,4'-trisubstitution showed high curativity toward P. berghei but were phototoxic. The most active compound was the 6,8,4'-trichloro-3-fluoro compound 7, and it appears very unlikely that its animal phtotoxicity would carry over into man and inhibit usefulness (p.37[2]). Earlier work begun under the Office of Ordinance Research offered a possible route to 3-substituted 2-aryl quinolines starting from suitably substituted cis-chalcones. With partial support from National Science Foundation grants to REL, and encouraged by possible usefulness here, this work was completed. (p. 50).

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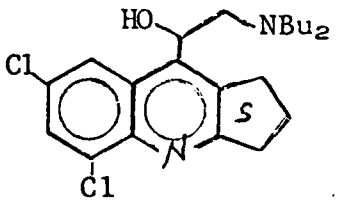
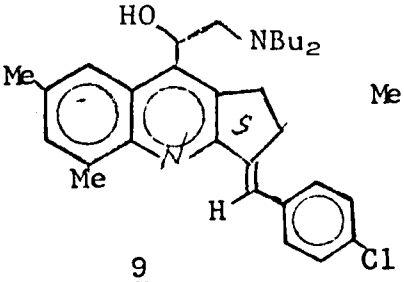
Part 7. The 6,8-dichloro-4-quinoline aminoalcohol with a 2,3-trimethylene fused ring, 8, proved to be moderately active and non-phototoxic in animals (p. 55). A unique 6,8-dimethyl analog of this, 9, the last compound made under the contract, is a 2-vinylog of 2-aryl-4-quinoline aminoalcohols, which carries a p-chlorostyryl group developed at the quinoline position-2 and extruding as a part of the rigid 2,3-tricarbon fused ring. This was highly curative in spite of the relatively poor auxopharmocophoric quality of the 6,8-dimethyls (as compared with 6,8-dichloro of the primary target analog, the synthesis of which was not completed[#c]). It was non-phototoxic in animals and was chosen for clinical trials on man (a project now shelved) (p.37). A sample of the simpler 2-styril analog 10 without the 2,3-tricarbon fused ring has since been made (1974) and submitted to WRAIR for test.



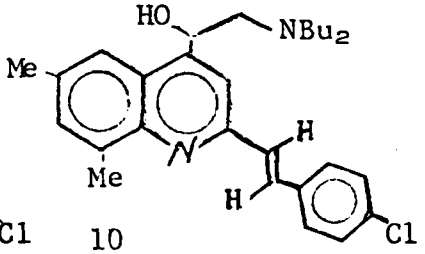
8

Moderately active; phototoxic in animals.



9

Highly curative; non-phototoxic in animals.



10

Part 1. 4-quinoline Aminoalcohols with and without 2-Aryl.

Communication to the Editor

Reprinted from the JOURNAL OF HETEROCYCLIC CHEMISTRY, 4, 459 (1967).

Department of Chemistry, University of Virginia

Pyridyl Ketones by Addition of Pyridyllithium to Carboxylic Acids. A New Synthesis of α-(2-Piperidyl)-2-aryl-4-quinolinemethanols (1)

D. W. Boykin, A. R. Patel, R. E. Lutz, and A. Burger

Antimalarials. I.

Sir:

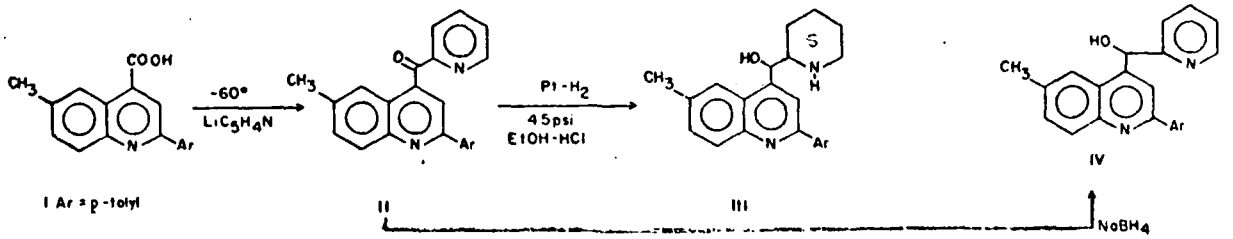
Resurgence of the malaria problem led us to synthesize a number of the title compounds, a type which had previously been made by a cumbersome 6-step synthesis from the corresponding quinoline-4-carboxylic acids (2). We now report a new and more convenient 2-step synthesis by which we have made fifteen α-(2-piperidyl)-2-aryl-quinolinemethanols in the 6-methyl, 8-methyl, 6,8-dimethyl and 8-trifluoromethyl series (*cf.* III). Also, by a variant in the second step, we have made twenty α-(2-pyridyl) analogs of type IV which represent a new class of potential synthetic medicinals, but which appear to be inactive toward malaria (*1b*).

In the example illustrated below the first step involves conversion of 2-*p*-tolylquinoline-4-carboxylic acid (I) by 2-pyridyllithium into 2-pyridyl ketone II. This reaction represents the first pyridyl ketone synthesis by addition of α-pyridyllithium to a carboxylic acid. The second step in the synthesis is controlled reduction of II. Catalytic hydrogenation specifically reduces the carbonyl and pyridyl groups and gives α-piperidylquinolinemethanol III; whereas, sodium borohydride reduces only the carbonyl group of II and gives the α-(2-pyridyl)quinolinemethanol IV. These reactions should find wide application in the alkaloid and synthetic medicinal fields.

Addition of 2 moles of α-pyridyllithium (3) at -60° to acid I followed by hydrolysis gave pyridyl ketone II; 60%; m.p. 142-143° (4,5). The structure is supported by: ν max (KBr), 1670 cm^{-1} (C=O); λ max (EtOH), 268, 344 mμ (2-arylquinoline type); nmr (deuteriochloroform), 1H signal at 1.3 τ characteristic of pyridine α-hydrogens.

Hydrogenation with platinum oxide of ketone II at 45 psi in ethanol containing 2 moles of hydrochloric acid, reduced the carbonyl and pyridyl groups, but not the quinoline nucleus. Only one of the two possible diastereoisomeric α-(2-piperidyl)quinolinemethanols III was isolated; 56%; m.p. 214-216° (4); λ max (EtOH), 267, 330, 339 mμ, ν max (KBr), *ca.* 3300 cm^{-1}; 2550-2750 cm^{-1}; nmr (deuteriochloroform), no signal at 1.3 τ, 1H doublet at 4.6 τ assignable to carbinol α-H, broad 3H and 6H multiplets at 6.5 and 8.4 τ, assigned to α-piperidyl and to β- and γ-piperidyl protons, respectively. The structure III was verified by infrared identity and mmp with a sample synthesized from I by the old route (2).

Reduction of only the carbonyl group of the 2-pyridyl ketone II by sodium borohydride afforded α-(2-pyridyl)-quinolinemethanol IV; 90%; m.p. 176-177.5° (4); ν max (KBr), 3200 cm^{-1}; λ max (EtOH), 268, 329, 339 mμ; nmr (deuteriochloroform), 1.4 τ, 4.5 τ (1H signals).



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(1a) Supported by the Walter Reed Army Institute of Research, Contract No. DA-49-193-MD-2955. (b) Antimalarial testing is in progress.

(2a) A. D. Ainly and H. King, *Proc. Roy. Soc.* (London), 125B, 60 (1938). (b) M. M. Rapport, A. E. Senear, J. F. Mead and J. B. Koepfli, *J. Am. Chem. Soc.*, 68, 2697 (1946). (c) R. F. Brown and 12 co-workers, *ibid.*, 68, 2705 (1946). (d) *cf.* α-Dialkylaminomethyl-2-aryl-4-quinolinemethanols; R. E. Lutz and 13 co-workers, *ibid.*, 68, 1813 (1946).

(3) J. P. Wibaut, A. P. DeJonge, H. G. P. Van Der Voort, and P. Ph. H. L. Otto, *Rec. Trav. Chim.*, 70, 1054 (1951).

(4) All new compounds gave correct elemental analyses.

(5) Addition of methyllithium to I gives the corresponding methyl ketone (80%) [*cf.* C. Tegner, *Acta. Chem. Scand.*, 6, 782 (1952)] and bromination gave the α-bromo ketone. These reactions were substituted for the conversion of I to the acid chloride, the hazardous large scale diazomethylation, and hydrobromination, which were formerly used in the synthesis of α-dialkylaminomethyl-2-aryl-4-quinolinemethanols (2d).

Received May 29, 1967 Charlottesville, Virginia 22901

[Reprinted from the Journal of Medicinal Chemistry, 11, 273 (1968).]

Antimalarials. IV.[1] A New Synthesis of α-(2-Pyridyl)- and α-(2-Piperidyl)-2-aryl-4-quinolinemethanols

D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz

Cobb Chemical Laboratory, University of Virginia, Charlottesville, Virginia 22901

Received November 14, 1967

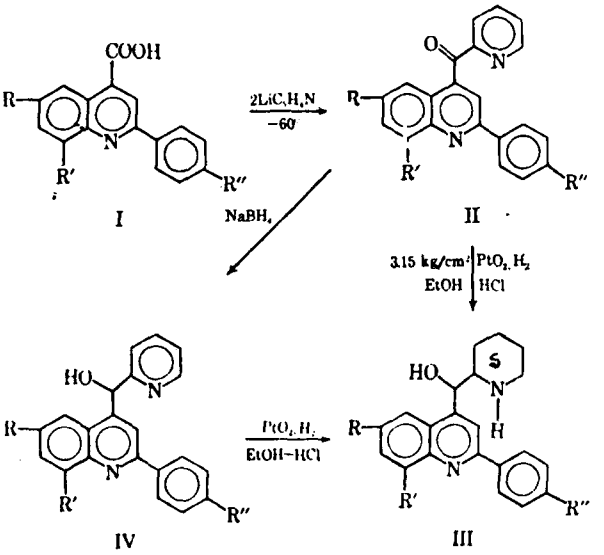
New convenient syntheses of α-(2-pyridyl)- and α-(2-piperidyl)-2-aryl-4-quinolinemethanols are reported. The key steps involve addition of pyridyllithium to quinoline-4-carboxylic acids and subsequent one-step selective catalytic S H hydrogenation of the ketopyridyl system to the α-piperidylmethanol. All of the α-piperidylmethanols were highly active against *Plasmodium berghei* in mice but were phototoxic, whereas the α-pyridyl analogs were considerably less phototoxic but were inactive.

This work is an extension of investigations carried out during the World War II antimalarial effort.[2] Earlier results had shown that 4-quinolylamino alcohols, particularly with a 2-aryl substituent as a deterrent to metabolic inactivation,[3] possessed considerable antiplasmodial activity against avian infections.[2,4,5]

α-Pyridyl- and α-Piperidylquinolinemethanols.—In a recent preliminary communication[1a] we have reported new syntheses for the title compounds. We now describe the details of the methods in full and report the antiplasmodial properties of these compounds.

The previous method for preparing α-piperidylquinolinemethanols was a tedious and cumbersome six-step synthesis starting from quinoline-4-carboxylic acids.[4] The new synthesis which we have developed is a convenient two-step process which also starts from quinoline-4-carboxylic acid (see Scheme I). The initial step involves conversion of the quinoline-4-carboxylic acid (I) by 2-pyridyllithium into the 2-pyridyl ketone II (Table I). The second step is the selective reduction of the 2-pyridyl and carbonyl groups of II by hydrogenation in acid solution over PtO_2 which produces the α-piperidylquinolinemethanols (III) (Table III). Recent reports of similar catalytic reductions include the selective reduction of the pyridine nucleus in 2-(2-pyridyl)-1,2-diarylalkanols[6]

Scheme I



and reduction of the pyridine portion of a quinoline ring system.[7]

In the conversion II → III, the selectivity of reduction presumably arises from selective protonation of the α-pyridyl ring which enhances the susceptibility of that ring toward reduction. The presumption of preferential protonation of the α-pyridyl ring is based upon steric considerations. Indeed, the hydrobromides of many 2,8-disubstituted quinolines cannot be obtained, presumably because of this effect,[2] which demonstrates the sensitivity of protonation to steric effects by substituents adjacent to the ring nitrogen. The reduction of II probably proceeds stepwise, first by reduction of the carbonyl group which is in conjugation with the imino groups of the pyridyl and quinolyl rings, followed by preferential reduction of the pyridyl ring. Ih sup-

(1) (a) Part I: D. W. Boykin, Jr., A. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 459 (1967). (b) Part III: A. Burger and S. N. Sawhney, *J. Med. Chem.*, **11**, 270 (1968). (c) Supported by U. S. Army Medical Research and Development Command, Contract No. DA-49-193-MD-2955, *Contribution No. 311 to the Army Research Program on Malaria* (Part I, No. 309). A. Burger and R. E. Lutz co-investigators.

(2) R. E. Lutz, *et al.*, *J. Am. Chem. Soc.*, **68**, 1813 (1946).

(3) R. T. Williams, "Detoxication Mechanisms," John Wiley and Sons, Inc., New York, N. Y., 1959, p 655.

(4) A. D. Ainley and H. King, *Proc. Roy. Soc.* (London), **B126**, 60 (1938); (b) M. M. Rapport, A. E. Senear, J. F. Mead, and J. B. Koepfli, *J. Am. Chem. Soc.*, **68**, 2697 (1946); (c) R. F. Brown, *et al.*, *ibid.*, **68**, 2705 (1946).

(5) F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," J. W. Edwards, Ann Arbor, Mich., 1946.

(6) J. H. Burckhalter, W. D. Dixon, M. L. Black, R. D. Westland, L. M. Werbel, H. A. DeWald, J. R. Dice, G. Rodney, and D. H. Kaump, *J. Med. Chem.*, **10**, 565 (1967).

(7) J. G. Cannon, S. A. Lazaris, and T. A. Wunderlich, *J. Heterocycl. Chem.*, **4**, 259 (1967).

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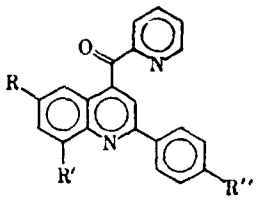
TABLE I[a]

2-PYRIDYL 2-ARYL-4-QUINOLYL KETONES (III)

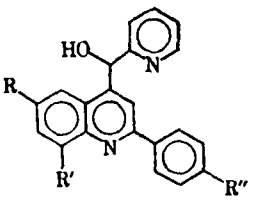


No.	R	R′	R″	Mp, °C	Yield, %	Formula	Analyses
1	CH_3	CH_3	H	143–145	76	$C_{23}H_{18}N_2O$	C, H
2	CH_3	CH_3	CH_3	144–145	81	$C_{24}H_{20}N_2O$	C, H
3	CH_3	CH_3	OCH_3	146–147	68	$C_{24}H_{20}N_2O_2$	C, H
4[b]	CH_3	CH_3	Cl	175–176	65	$C_{23}H_{17}ClN_2O$	C, H
5	CH_3	CH_3	F	140.5–142	62	$C_{23}H_{17}FN_2O$	C, H
6	H	CF_3	H	145–146.5	72	$C_{23}H_{15}F_3N_2O$	C,[c] H
7	H	CF_3	CH_3	162.5–163.5	74	$C_{24}H_{17}F_3N_2O$	C, H
8	H	CF_3	OCH_3	162–163	66	$C_{24}H_{17}F_3N_2O_2$	C, H
9	H	CF_3	Cl	192–193	85	$C_{23}H_{14}ClF_3N_2O$	C, H
10	H	CF_3	F	206–207	60	$C_{23}H_{14}F_4N_2O$	C, H
11	CH_3	H	H	140.5–142	45	$C_{23}H_{18}N_2O$	C, H
12	CH_3	H	CH_3	142–143	60	$C_{24}H_{20}N_2O$	C, H, N
13	CH_3	H	OCH_3	147–148	47	$C_{24}H_{20}N_2O_2$	C, H
14	CH_3	H	Cl	192.5–193	50	$C_{23}H_{17}ClN_2O$	C, H
15	CH_3	H	F	155–156.5	49	$C_{23}H_{17}FN_2O$	C, H, N
16	OCH_3	H	CH_3	166–167	45	$C_{24}H_{20}N_2O_2$	C, H
17	H	CH_3	H	130.5–132.5	84	$C_{22}H_{16}N_2O$	C, H
18	H	CH_3	CH_3	142.5–144	59	$C_{23}H_{18}N_2O$	C, H
19	H	CH_3	OCH_3	143–145	66	$C_{23}H_{18}N_2O_2$	C, H
20	H	CH_3	Cl	144–146	70	$C_{22}H_{15}ClN_2O$	C, H
21[d]	H	CH_3	F	141.5–142.5	75	$C_{22}H_{15}FN_2O$	...
22	F	H	CH_3	172–174	49	$C_{22}H_{15}FN_2O$	C, H

[a] Unless otherwise noted solvent of recrystallization was EtOH. [b] Recrystallization solvent MeCN. [c] C: calcd, 69.84; found, 69.40. [d] This compound was used directly without analysis.

TABLE II

α,2-PYRIDYL-4-QUINOLINEMETHANOLS (IV)



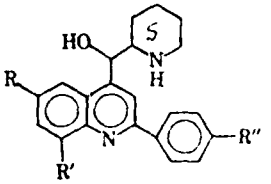
No.	R	R′	R″	Mp, °C	Yield, %	Recrystn solvent	Formula	Analyses
23	CH_3	CH_3	H	163–164.5	80	MeCN–$CHCl_3$	$C_{23}H_{20}N_2O$	C, H, N
24	CH_3	CH_3	CH_3	193–194	70	EtOH	$C_{24}H_{22}N_2O$	C, H, N
25	CH_3	CH_3	OCH_3	185–187	90	EtOH	$C_{24}H_{22}N_2O_2$	C, H, N
26	CH_3	CH_3	Cl	167–169	87	EtOH	$C_{23}H_{19}ClN_2O$	C, H, N
27	CH_3	CH_3	F	173–175	87	EtOH	$C_{23}H_{19}FN_2O$	C, H, N
28	H	CF_3	H	193–194.5	93	MeCN	$C_{23}H_{15}F_3N_2O$	C, H, N
29	H	CF_3	CH_3	178–179.5	85	EtOH	$C_{24}H_{17}F_3N_2O$	C, H, N
30	H	CF_3	OCH_3	210–212	80	EtOAc	$C_{24}H_{17}F_3N_2O_2$	C, H, N
31	H	CF_3	Cl	214–216 dec	74	EtOH	$C_{23}H_{14}ClF_3N_2O$	C, H, N
32	H	CF_3	F	178–181	95	EtOH	$C_{23}H_{14}F_4N_2O$	C, H, N
33	CH_3	H	H	180–180.5	80	EtOH	$C_{23}H_{18}N_2O$	C, H, N
34	CH_3	H	CH_3	176–177.5	92	EtOH	$C_{24}H_{20}N_2O$	C, H, N
35	CH_3	H	OCH_3	191–192	95	EtOH	$C_{24}H_{20}N_2O_2$	C, H, N
36	CH_3	H	Cl	184–186	85	EtOH	$C_{23}H_{17}ClN_2O$	C, H, N
37	CH_3	H	F	176–178	70	EtOH	$C_{23}H_{17}FN_2O$	C, H, N
38	OCH_3	H	CH_3	178–180	80	EtOH	$C_{24}H_{20}N_2O_2$	C, H, N
39	H	CH_3	H	145–147	86	MeCN–$CHCl_3$	$C_{23}H_{18}N_2O$	C, H, N
40	H	CH_3	CH_3	174–175	92	EtOH	$C_{24}H_{20}N_2O$	C, H
41	H	CH_3	OCH_3	154–156	90	MeCN	$C_{24}H_{20}N_2O_2$	C, H
42	H	CH_3	Cl	174–175.5	83	MeCN	$C_{23}H_{17}ClN_2O$	C, H
43	H	CH_3	F	139–141[a]	95	EtOH	$C_{23}H_{17}FN_2O$	C, H

[a] Sinters at 128–130°.

-9-

TABLE III[a]

α,2-PIPERIDYL-4-QUINOLINEMETHANOLS (III)



No.	R	R'	R''	Mp, °C	Yield, %	Formula	Analyses	Antimalarial act.[b] Dose, mg/kg	Cures
44	CH_3	CH_3	CH_3	220–221	46	$C_{24}H_{28}N_2O$	C, H, N	160	1
45	CH_3	CH_3	OCH_3	200–201	43	$C_{24}H_{28}N_2O_2$	C, H, N	40	0[c]
								80	2[d]
46	CH_3	CH_3	Cl	212–214	19	$C_{23}H_{25}ClN_2O$	C, H, N	20	1
								40	3
47	CH_3	CH_3	F	175–177[e]	29	$C_{23}H_{25}FN_2O$	C, H, N	40	0[f]
								80	2
48	H	CF_3	H	197–198	46	$C_{22}H_{21}F_3N_2O$	C, H, N	20	2
49	H	CF_3	CH_3	195–197	75	$C_{23}H_{23}F_3N_2O$	C, H, N	20	0[g]
								40	2
50	H	CF_3	OCH_3	182–184	53	$C_{23}H_{23}F_3N_2O_2$	C, H, N	20	1
								40	3
51	H	CF_3	Cl	181–182	38	$C_{22}H_{20}ClF_3N_2O$	C, H, N	20	5
52	CH_3	H	H	179–181[h]	38	$C_{22}H_{24}N_2O$	C, H, N	640[i]	1
53	CH_3	H	CH_3	214–216[j]	56	$C_{23}H_{26}N_2O$	C, H, N	640	0[k]
54	CH	H	OCH_3	206–207	58	$C_{23}H_{26}N_2O_2$	C, H, N	160	0[l]
								320	2
55	CH_3	H	Cl	217–219	12	$C_{22}H_{23}ClN_2O$	H, N; C[m]		
56	H	CH_3	H	188–189[n]	31	$C_{22}H_{24}N_2O$	C, H, N	80	1
								160	3
57	H	CH_3	CH_3	175–175.5	32	$C_{23}H_{26}N_2O_2$	C, H, N	80	1[o]
								320	4
58	H	CH_3	Cl	169–171	23	$C_{22}H_{23}ClN_2O$	C, H	20	2
59	H	CH_3	F	182.5–184	26	$C_{22}H_{23}FN_2O$	C, H	40	2

[a] Recrystallization solvent MeCN. [b] Antimalarial test results were supplied through the courtesy of Dr. David P. Jacobus of the Walter Reed Army Institute of Research. Tests were carried out in groups of five mice infected with *Plasmodium berghei*. The drugs were injected in doses of 20, 40, 80, 160, 320, and 640 mg/kg. Unless shown all the animals were cured at higher doses up to the maximum of 640 mg/kg. Enhancement in survival time of treated animals is regarded as evidence of antimalarial activity. A compound is considered to be active if the mean survival time of the treated group is more than double the mean survival time of the control group (7.0 ± 0.5 days); it is said to be curative when the animal survives up to 60 days. [c] Active: increased survival time 7 days. [d] Two cures at 160 mg/kg. [e] Softens 140°. [f] Increased survival time 9.6 days. [g] Increased survival time 7.8 days. [h] Lit.[9] 182.5–182.9°. [i] Inactive below this dosage. [j] Softens 150°. [k] Increased survival time 9.6 days. [l] Increased survival time 9.2 days. [m] C: calcd, 72.02; found, 71.47. [n] Lit.[9] 187.8–188.3°. [o] One cure at 160 mg/kg.

port of the suggested steps are the following: (a) in a few cases the hydrogenation was interrupted before completion and the first-stage reduction product, the α-pyridyl alcohol, was isolated; and (b) reduction of the 2-pyridyl ring of the alcohol **29**[9] proceeded smoothly under the conditions which reduce the ketones II to III.

That the nucleus of the quinoline ring in the ketones II was unaffected by the catalytic reductions was demonstrated by spectral methods. Uv absorption characteristics of 2-arylquinolines were obtained for the reduction products III. The nmr spectra obtained from III were as expected for the type. In our previous report[1a] the spectral data and their interpretations for a typical example of III were presented.

The ultimate validation of the new synthetic scheme as an unambiguous route to compounds of type III rests in the identity of samples of **53** obtained by both the new method and by the older method.[4] Further support comes from the compounds **52** and **56** which were prepared by the new scheme and have physical properties which are in accord with those reported in the literature for these compounds synthesized by the older route.[9]

Two apparent exceptions have been observed; compound **15** seemingly undergoes reduction beyond the desired stage III[10] and **19** gave intractable resins. Thus, it is necessary to confirm the structure of each new compound obtained by this new method.

Reductions of the pyridyl ketones II by sodium borohydride produces in good yields the α-2-pyridylquinolinemethanols IV (Table II). The structure of the resulting compounds is based upon the method of synthesis and their spectral properties which are distinctive and corroborative (*cf.* ref 1a).

Biological Activity. The compounds of types III and IV were tested for antimalarial activity against *Plasmodium berghei* in mice by the method of Rane.[11] All of the α-pyridylquinolinemethanols of type IV (Table II) were inactive in this test, but they showed phototoxicity. However, all of the α-piperidylquino-

(9) E. R. Buchman and D. R. Howton, *J. Am. Chem. Soc.*, **68**, 2718 (1946).

(10) This requires further investigation.

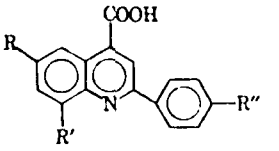
(11) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(8) Aryl = phenyl as used only for the compounds listed in this table.

-10-

TABLE IV[a]

SUBSTITUTED CINCHONINIC ACIDS



I

No.	R	R′	R″	Mp, °C	Yield, %	Formula	Analyses
60	CH_3	H	CH_3	240–244 dec	90.9	$C_{19}H_{17}NO_2$	C, H
61	CH_3	H	OCH_3	237–238[b]	77.3	$C_{19}H_{17}NO_3$	C, H
62	CH_3	H	Cl	272–274[c]	85.1	$C_{18}H_{14}ClNO_2$	C, H
63	CH_3	H	F	225–228	92.4	$C_{18}H_{14}FNO_2$	C, H[d]
64[e]	CH_3	CH_3	CH_3	244–246	75.2	$C_{20}H_{19}NO_2$	C, H
65	CH_3	CH_3	OCH_3	250–252[f]	70.2	$C_{20}H_{19}NO_3$	C, H
66	CH_3	CH_3	F	246–251	70.7	$C_{19}H_{16}FNO_2$	C, H
67	H	CF_3	H	260–265 dec	88.3	$C_{17}H_{10}F_3NO_2$	C, H
68	H	CF_3	CH_3	268–271 dec	83.5	$C_{18}H_{12}F_3NO_2$	C, H
69	H	CF_3	OCH_3	238–241 dec	86.1	$C_{18}H_{12}F_3NO_3$	C, H
70	H	CF_3	Cl	265–275	94.4	$C_{17}H_9ClF_3NO_2$	C, H
71	H	CF_3	F	257–269	89.5	$C_{17}H_9F_4NO_2$	C, H
72	OCH_3	H	CH_3	242–245	75.0	$C_{19}H_{17}NO_3$	C, H
73	OCH_3	H	OCH_3	242–245	89.9	$C_{19}H_{17}NO_4$	C, H
74	OCH_3	H	F	223–230	59.4	$C_{17}H_{12}FNO_3$	C, H
75	F	H	CH_3	274–275	92.5	$C_{17}H_{12}FNO_2$	C, H
76	F	H	Cl	253–256	69.9	$C_{16}H_9ClFNO_2$	C, H
77	H	CH_3	CH_3	245–249	78.1	$C_{19}H_{15}NO_2$	C, H
78	H	CH_3	F	201–206	83.2	$C_{17}H_{12}FNO_2$	C, H

[a] Recrystallized from EtOH. [b] T. Kaku [*J. Pharm. Soc. Japan*, **545**, 577 (1927)] reported 230–231°. [c] N. P. Buu-Hoi R. Royer, N. D. Xuong, and P. Jacquignon [*J. Org. Chem.*, **18**, 1209 (1953)]. [d] H: caled, 4.30; found, 4.95. [e] A. H. Crosby, M.S. Thesis, University of Virginia, 1950, p 11. [f] Lit.[b] 239°.

linemethanols of type III were highly active but all consistently caused serious photosensitization in mice. The antimalarial test data for these compounds are shown in Table III. Of these α-piperidylquinolinemethanols only two have been tested previously.[5] The "quinine equivalents" of **52** ranged from 0.3 against *P. gallinaceum* in chicks to 10.0 against *P. cathemerium* in ducks, and that of **56** from 0.6 against *P. gallinaceum* in chicks to 8.0 against *P. lophurae* in ducks.

Experimental Section

Melting points were obtained on a Thomas–Hoover or a Fischer-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., and Micro-Tech Laboratories, Inc. Satisfactory uv and ir spectra were recorded for each compound listed in the tables. Nmr spectra were obtained for all compounds of type IV which were soluble in $CDCl_3$ or DMSO-d_6; random nmr determinations were made on all the other types. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

2-Pyridyl Ketones (II). 2-Pyridyl 2-(*p*-Tolyl)-6-methyl-4-quinolyl Ketone (See Table I).—The pyridyllithium (from 18.0 g of 2-bromopyridine in 100 ml of Et_2O) was prepared essentially by the published method.[12,13] To the stirred solution of 2-pyridyllithium under N_2 and at −60° was added rapidly (1–2 min) finely ground 6-methyl-2-(*p*-tolyl)quinoline-4-carboxylic acid (10.0 g) *via* a powder funnel. The addition of acid was followed after 5 min of stirring by the addition of 100 ml of anhydrous Et_2O. The reaction mixture was allowed to stir for 3 hr at −60° under N_2, after which time the Dry Ice bath was removed and the solution was allowed to warm to 0–5°. At this temperature the reaction mixture was hydrolyzed cautiously by adding 100 ml of moist Et_2O to the stirred solution, followed by 100 ml of H_2O. The resulting heterogenous mixture was stirred for 2–3 min and the layers were separated. The Et_2O solution (normally dark red) was evaporated under reduced pressure and the resulting residue was taken up in hot EtOH and allowed to crystallize.

Piperidylquinolinemethanols (III). α-(2-Piperidyl)-2-(*p*-tolyl)-6-methyl-4-quinolinemethanol (See Table III).—2-Pyridyl 2-(*p*-tolyl)-6-methyl-4-quinolyl ketone (2 g) was dissolved in *ca.* 200 ml of hot absolute EtOH to which was added 2 ml of concentrated HCl (37–38%, sp gr 1.19). The EtOH solution was cooled and hydrogenated over 0.2 g of PtO_2 (Englehard) at 3.15 kg/cm². Absorption of H_2 stopped essentially in *ca.* 1 hr. The catalyst was removed by filtering over Celite and the EtOH solution was concentrated to *ca.* 30 ml by evaporation under reduced pressure and was poured into a stirred $NaHCO_3$ solution. The resulting aqueous suspension of the free base was extracted with Et_2O (*ca.* 300 ml). The Et_2O was evaporated and the residue taken up in MeCN (25–40 ml).

Frequently the crude product oils out and/or is quite impure, hence several (six ten) recrystallizations are required to obtain analytical samples. In a few runs a small amount of MeCN-insoluble, high-melting fibrous material was obtained, which was removed by filtration.

Pyridylquinolinemethanols (IV). α-(2-Pyridyl)-2-(*p*-tolyl)-6-methyl-4-quinolinemethanol (See Table II).—To a stirred slurry of 2.0 g of the pyridyl ketone **18** in 50 ml of EtOH was added 0.2 g of $NaBH_4$. The mixture was stirred at room temperature for 1 hr and poured into 400 ml of H_2O, and the solid was filtered. Recrystallization was from EtOH.

Ethyl 6-Methyl-2-(*p*-tolyl)cinchoninate.—6-Methyl-2-(*p*-tolyl)-4-*cinchominic acid* (0.08 mole, 24.18 g) was suspended in 450 ml of absolute EtOH and 20 ml of concentrated H_2SO_4 was added. The mixture was refluxed for 24 hr, cooled, and then poured onto ice water and extracted with Et_2O. The Et_2O extract was washed (aqueous Na_2CO_3, H_2O) and after drying ($MgSO_4$) the Et_2O was removed under reduced pressure. The yield of product was 20 g, mp 74–76°. *Anal.* ($C_{20}H_{19}NO_2$) C, H, N.

α-(2-Piperidyl)-2-(*p*-tolyl)-6-methyl-4-quinolinemethanol.[14]—

(12) J. P. Wibaut, A. P. De Jonge, H. G. P. Van Der Voort, and P. Ph. H. L. Otto, *Rec. Trav. Chim.*, **70**, 1043 (1951).

(13) It is important that reactants and solvents are dry. The pyridyllithium solution should be prepared and maintained at a temperature at [illegible]

(14) F. E. Bachman, H. Sargent, T. C. Myers, and D. R. [illegible] *J. Am. Chem. Soc.*, **68** [illegible]

-11-

To a solution of the foregoing ester (0.06 mole, 18.32 g) and ethyl 6-benzamidocaproate[15] (0.061 mole, 16.06 g) in 50 ml of dry C_6H_6, $NaNH_2$ (0.075 mole, 2.93 g) was added. The mixture was heated at 90° with vigorous stirring for 24 hr. After cooling the mixture to 50°, 32 ml of concentrated H_2SO_4 in 50 ml of H_2O was added and refluxing was continued for 65 hr. The C_6H_6 was then distilled off azeotropically and the residue was made alkaline with 30% aqueous NaOH keeping the temperature below 40°. The mixture was then extracted with C_6H_6. After drying ($MgSO_4$) the solvent was removed under reduced pressure. The ir spectrum of the solid residue indicated that the N-benzoyl group was not cleaved. The material was therefore suspended again in a solution of 30 ml of concentrated H_2SO_4 in 50 ml of H_2O and the mixture was refluxed for 64 hr. After cooling it was made alkaline as before and extracted with C_6H_6. The dried C_6H_6 solution upon concentration *in vacuo* left an oil to which 23 g of 48% HBr was added. Upon standing for a short while a yellow precipitate was obtained and filtered: the yield of 6-[6-methyl-2-(*p*-tolyl)cinchoninyl]-*n*-amylamine dihydrobromide was 5.5 g (34% based on recovered acid).[15]

The aqueous alkaline phase was acidified with concentrated HCl and the resulting precipitate was filtered, washed with a little EtOH, and dried. The weight of recovered 6-methyl-2-(*p*-tolyl)-4-cinchoninic acid from the unreacted ethyl ester was 7.8 g.

The foregoing amine dihydrobromide (0.008 mole, 4 g) was dissolved in hot 18% HBr and treated rapidly with a solution of Br_2 (0.008 mole, 1.28 g) in an equal volume of 48% HBr. The crude product was filtered and dispersed in 40 ml of boiling 95% EtOH, and H_2O was added until a clear solution resulted. Cooling gave a light yellow precipitate. Concentration of the mother liquor yielded some additional product. The total yield of 6-bromo-6-[6-methyl-2-(*p*-tolyl)cinchoninyl]-*n*-amylamine dihydrobromide was 3.95 g (84%).

The foregoing product (1.5 g) was dissolved in 50 ml of 95% EtOH and 7 ml of 14% aqueous Na_2CO_3 was added. The mixture was shaken for 1 hr in a stoppered bottle and then hydrogenated over 20 mg of PtO_2 in a Parr hydrogenation apparatus. The reaction mixture was filtered and washed (EtOH, hot $CHCl_3$). The solvents were removed *in vacuo*. The residue was dissolved in hot $CHCl_3$ and filtered. Evaporation of the solvent left a brown residue. This was dissolved in absolute EtOH and the solution was saturated with dry HCl. After standing for a short while, Et_2O was added and the precipitate was filtered to yield 0.5 g of the hydrochloride. A small amount of this salt was converted into the free base **53**.

The ir spectra of the free base **53** and its hydrochloride salt were identical with those of the products obtained by catalytic reductions of the pyridyl ketone.

2-Aryl-4-quinolinecarboxylic Acids (Cinchoninic Acids) (I) (Table IV).—All of the substituted cinchophens required as starting material were synthesized by the Pfitzinger[16] condensation. In general, it was found that better yields were obtained when the mixtures of the appropriate isatins and substituted acetophenones in EtOH–KOH were refluxed for 30 hr; shorter periods of time gave poorer yields.

Acknowledgment.—The authors wish to thank Professor A. Burger for fruitful discussion before and during the course of this work.

(15) This intermediate and the ones which follow en route to **50** were used directly in the next synthetic step without characterization; *cf.* ref 9 and 14.

(16) W. Pfitzinger, *J. Prakt. Chem.*, **56**, 283 (1897).

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Antimalarials. 6. Some New α-Alkylaminomethyl-4-quinolinemethanols[1]

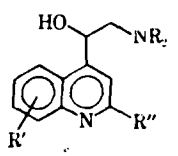
A. R Patel,[2] C. J. Ohnmacht,[2] D. P. Clifford,[2] A. S. Crosby,[3] and R. E. Lutz*

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

Received August 10, 1970

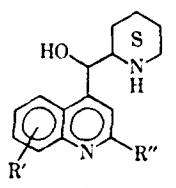
Nine new 4-quinoline amino alcohols were synthesized for antimalarial tests. Successful approaches for introducing the α-pyridyl group were addition of the 4-quinolyllithium to 2-pyridyl nitrile and to 2-pyridaldehyde. Selective hydrogenation of 8-trifluoromethyl-4-quinolyl 2-pyridyl ketone gave low yields of the quinoline α-pyridylmethanol and large yields of the tetrahydroquinoline. 7-Trifluoromethylcinchoninic acid added 2-pyridyllithium giving low yields of both the ketone and the α,2-dipyridyl ketone; the ester gave the pyridyl ketone in good yield but subsequent selective hydrogenation was unsuccessful.

A large number of 2-aryl-4-quinoline amino alcohols of types **1** and **2** (R″ = aryl)[4,5] have proved to be active or curative against *Plasmodium berghei* in mice,[6] but they were highly phototoxic, due possibly, it has been postulated,[7] to enhancement of nuclear conjugation by the coplanar 2-aryl group. Substitution of CF_3 for the 2-aryl group produced only moderately active antimalarials and these were moderately phototoxic.[5] This paper deals with syntheses and testing of 9 new analogs and investigation of some potentially useful procedures.



1

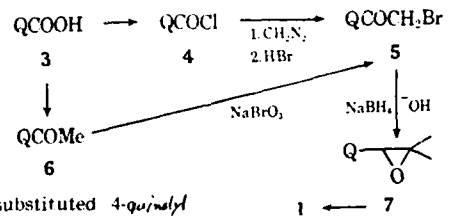
	R	R′	R″
a	Et	6,8-Me_2	*p*-tolyl
b	Bu	6,8-Me_2	*p*-tolyl
c	Et	7-Cl	H
d	Bu	7-CF_3	H



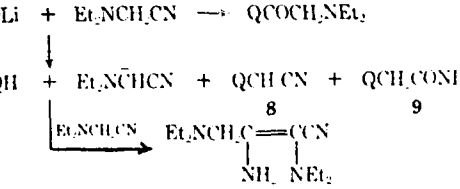
2

	R′	R″
a	6-F	*p*-tolyl
b	6-F	CF_3
c	8-H	CF_3
d	8-CF_3	H

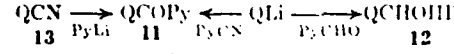
α-Dialkylaminomethyl-4-quinolinemethanols (1).— The recent and useful modification of the classical synthetic procedures[4] involves the facile and high yield reaction of a dialkylamine with the ethylene oxide **7** which is made either from the appropriate aldehyde, if available,[9] or from the bromo ketone **5** by $NaBH_4$ reduction and added base.[5c,10] An alternative route to the bromo ketone **5**, avoiding the use of CH_2N_2,[4] was through the Me ketone **6** which was prepared by addition of MeLi to the acid **3**. Bromination of **6** with $NaBrO_3$ in HBr[11] gave **5** in high yield, *e.g.*, 2-*p*-tolyl-6,8-dimethyl-4-acetylquinoline (**6a**, 72% from **3**) gave **5a** in 88% yield (66% from **3** which is a better yield than *via* **42**).[3] The bromination of **6a** directly in AcOH or by ammonium perbromide involved formation of considerable amounts of the dibromomethyl ketone as by-product.



Attempts toward a more direct introduction of the amino alcohol group into the quinoline through reaction of 2-trifluoromethyl-4-quinolyllithium[8] with MeCN or with diethylaminoacetonitrile were unsuccessful (not surprisingly[12]). Neither the Me nor the diethylaminomethyl 4-quinolyl ketones were isolated. Evidently extensive ionization and dimerization of both nitriles had occurred, and in the case of diethylaminoacetonitrile, there occurred considerable displacement of the NEt_2 group by the 4-quinolyl anion, presumably giving **8** and **9**. The structure of the one dimer characterized, namely **10**, is based on anal. and ir and nmr spectra.



α-(2-Piperidyl)-4-quinolinemethanols (2). - Of particular interest as potentially useful methods are the following. The addition of 6-chloro- and 6-methyl-2-trifluoromethyl-4-quinolyllithiums at −70° to 2-cyanopyridine gave the known α-(2-pyridyl)-4-quinolyl ketones **11**.[8] The addition of 2-PyLi to 6,8-dimethyl-4-cyano-2-trifluoromethylquinoline also gave **11**. Additions to 2-pyridaldehyde of 2-trifluoromethyl-4-quinolyllithium or its 6-Me derivative gave the corresponding known α-(2-pyridyl)-4-quinolinemethanols **12**.[3]



Py = 2-pyridyl

(1) This work, largely done prior to summer 1968, was supported by the U. S. Army Medical Research and Development Command, Office of the Surgeon General; Contract No. DA-49-193-MD-2955. Contribution No. 838 of the Army Program on Malaria, R. E. Lutz, Responsible Investigator.

(2) Postdoctoral Research Associates.

(3) A. L. Crosby, M.S. Thesis, University of Virginia, Charlottesville, Va, 1950.

(4) R. E. Lutz, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1813 (1946).

(5) (a) D. W. Boykin, Jr., A. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 159 (1967); (b) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, **11**, 273 (1968); (c) *cf.* C. J. Ohnmacht, F. Davis, and R. E. Lutz, *ibid.*, **14**, 17 (1971).

(6) T. S. Osdene, P. B. Russell, and L. Rane, *ibid.*, **10**, 431 (1967). Tests were performed by Dr. Leo Rane, and results were provided through the Walter Reed Army Institute of Research.

(7) W. E. Rothe and D. P. Jacobus, *ibid.*, **11**, 366 (1968).

(8) A. Burger and R. M. Pinder, *ibid.*, **11**, 267 (1968).

(9) W. C. Duncan, W. T. Colwell, C. R. Scott, and D. W. Henry, *ibid.*, **11**, 1222 (1968).

(10) E. R. Atkinson and V. J. Puttick, *ibid.*, **11**, 1223 (1968).

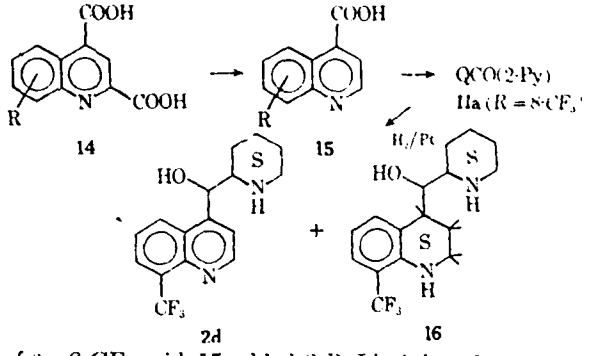
(11) J. W. Cook *et al.*, *J. Amer. Chem. Soc.*, **68**, 1831 (1946).

(12) E. L. Eliel and N. L. Allinger, *ibid.*, **75**, [illegible] (1953).

-13-

4-Quinoline Amino Alcohols without a 2 Substituent (1c,d, 2d).—Three examples of these compounds were made to test the effectiveness of Cl and CF_3 groups in the 7 position and of the CF_3 in the 8 position. These, without the 2-aryl group, were not expected to be seriously phototoxic.

Syntheses started from the corresponding isatins which were prepared following published procedures.[12] Pfitzinger condensations of these with pyruvic acid to the quinoline-2,4-dicarboxylic acids **14**[13] and selective thermal decarboxylations in $PhNO_2$ or Ph_2O gave the cinchoninic acids **15**.

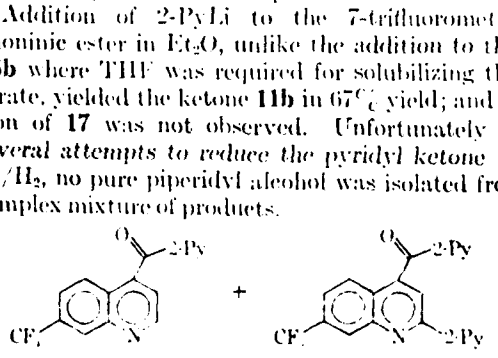


The 8-CF_3 acid **15** added 2-PyLi giving the pyridyl ketone **11a** (76%). This, using Pt/H_2 under a variety of conditions, gave at best only 4% of the target α-(2-piperidyl)methanol **2d**; the principal other product was the tetrahydroquinolyl analog **16** (46%). The unusually poor yield of **2d** might be attributed to decreased selectivity of protonation of **11a** at the pyridyl N because of the absence of the 2 substituent and/or the *absence of the deterrent steric effects by 2 substituents* on hydrogenation of the quinoline N ring.

An attempted preparation of **2d** by the 6-step Ainly and King synthesis[15] failed in the last stages.

Treatment of 7-trifluoromethylcinchoninic acid (**15b**) with 2-PyLi at −70° in 30% THF–Et_2O gave the desired 2-pyridyl ketone **11b** but in only 16% yield. Also isolated in 12% yield was the diaddition product, α-pyridyl 2-(2-pyridyl)-7-trifluoromethyl-4-quinolyl ketone **17** which must have involved both addition of 2-PyLi at position 2 and oxidative aromatization of the resulting dihydroquinoline. These two compounds were characterized by anal. and nmr spectra.

Addition of 2-PyLi to the 7-trifluoromethylcinchoninic ester in Et_2O, unlike the addition to the acid **15b** where THF was required for solubilizing the substrate, yielded the ketone **11b** in 67% yield; and formation of **17** was not observed. Unfortunately in the *several attempts to reduce the pyridyl ketone* **11b** by Pt/H_2, no pure piperidyl alcohol was isolated from the complex mixture of products.



11b **17**

(13) (a) S. L. Holt and P. W. Sadler, *Proc. Roy. Soc.*, **148**, 481 (1958); (b) L. Smart, *J. Org. Chem.*, **28**, 3580 (1963); **21**, 160 (1956).

(14) A. L. Scovar, H. Sargent, J. F. Mead, and J. B. Koepfli, *J. Amer. Chem. Soc.*, **68**, 2605 (1946).

(15) A. D. Ainley and H. King, *Proc. Roy. Soc. Ser. B*, **125**, 60 (1938).

Since the α-(2-piperidyl)-7-trifluoromethyl-4-quinolinemethanol corresponding to **17** was not obtained, the α-dibutylaminomethyl analog **1d** was synthesized through the diazomethylation of the corresponding cinchoninic acid by standard procedures.[5,9,10]

7-Chlorocinchoninic acid (**15**, R = 7-Cl) did not give the desired ketones upon treatment with MeLi or 2-PyLi. The α-diethylaminomethyl-7-chloro-4-quinolinemethanol was therefore synthesized by the classical procedure employed earlier for the dihexyl analog.[16]

2-Substituted-α-(2-piperidyl)-4-quinolinemethanols (2).—Three of these, the 6-fluoro-2-*p*-tolyl and 6-fluoro-2-trifluoromethyl derivatives **2a** and **2b**, and the 8-fluoro-2-trifluoromethyl compound **2c**, were synthesized by known procedures.[5,8] In each case, as in the many analogous syntheses in this series, only one of the two possible diastereoisomeric racemates was isolated, presumably formed predominantly by stereospecific hydrogenation.[5c]

Biological Data.[c]—The antimalarial activities of compounds **1** and **2**, listed in Table I, were not outstanding. The most active, **1a** and **1b**, were partially curative at 640 mg/kg and active at 160 mg/kg. Only **1a** effected low but significant increase in survival time at 40 mg/kg. The one tetrahydroquinoline, **16**, was inactive.

TABLE I

ACTIVITIES[a] AGAINST *P. berghei* IN MICE[b]

Compd	640 mg/kg	160 mg/kg	40 mg/kg
1a	2C/29.1[c]	6.8	0.8
1b	2C/27.2[c]	16.7	2.9
1c	0.8	0.6	0.4
1d	8.5	0.1	0.1
2a	1.3	1.1	0.9
2b	9.1	3.5	0.7
2c	10.5	5.1	0.3
2d		5.9	0.5
16	0.5	0.3	0.3

[a] Figures are average increases in survival time (days) of infected mice (5 per test group) beyond that of untreated controls. [b] See ref 6. [c] Two cures and an average increase in survival time of 3 mice.

Experimental Section[17]

2-Aryl-4-acetylquinolines (6).—In a typical example, 9.5 g (0.031 mole) of powdered 2-*p*-tolyl-6-methylcinchoninic acid followed by 200 ml of dry Et_2O was rapidly added to a vigorously stirred soln of 0.087 mole of MeLi (from 1.2 g of Li and 14 g of MeI) in 120 ml of anhyd Et_2O under N_2. After stirring for 2 addl hr and hydrolysis and evapn of the ether layer, the residue was recrystd from abs EtOH: 8.1 g of **6b** (86%).

α-Bromomethyl 2-Aryl-4-quinolyl Ketones (5a d).—To a stirred refluxing soln of 2.75 g (0.01 mole) of **6b** in 25 ml of glacial AcOH, was added over 15 min, a soln of 1.60 g (0.01 mole) of Br_2 in 15 ml of glacial AcOH, with continued refluxing for 10 min. Upon cooling and pouring onto ice, the resulting ppt was washed with $NaHCO_3$ soln, and recrystd from abs EtOH: 2.0 g (56%).

(16) (a) N. H. Leake, Ph.D. Dissertation, University of Virginia, Charlottesville, Va., 1946, p 162; (b) R. E. Lutz, J. F. Codington, and N. H. Leake, *J. Amer. Chem. Soc.*, **69**, 1260 (1947).

(17) Instruments used were: Thomas-Hoover apparatus for mp, uncorr. Anal. were correct (±0.4%): Galbraith Lab, Inc., and Swartzkopf Microanalytical Lab. Vacuum sublimation of analytical samples was at 10–50° the respective mp. Satisfactory spectra were obtained, for structural determination where required, and randomly in other cases: ir, Perkin-Elmer 337, nmr, Hitachi, P. E. R20, mass spectrograph, Hitachi, P-E, RMU 6F.

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B. To a stirred slurry of 5.79 g (0.02 mole) of **6a** and 50 ml of glacial AcOH was added 1.01 g (0.0066 mole) of $NaBrO_3$ followed under heating at 100° by dropwise addition of 14 g of 48% HBr. The mixture was then poured onto ice-H_2O and the resulting ppt was recrystd from EtOH; 6.48 g (88%). The yield of **5b** by this method was 75%.

α-(Di-*n*-butylaminomethyl)-2-*p*-tolyl-6,8-dimethyl-4-quinolinemethanol·HCl (1b). A mixture of crude bromohydrin (11.1 g, 0.03 mole, obtained in 81% yield by AlO-*i*-Pr)$_3$ reduction of the bromo ketone **5a**[4,11]) and 19.5 g (0.015 mole) of *n*-Bu_2NH at 80–85° was stirred for 60 hr, cooled, and dild with dry Et_2O. After removing the pptd salt by filtration the soln was concd under reduced pressure and the unused *n*-Bu_2NH was then removed by vac distn. A soln of the residual viscous oil in a small amount of abs EtOH was cooled in ice and treated with ethereal HCl. The resulting ppt was recrystd from EtOH–Et_2O; 12.68 g (93%); **1a** was made similarly. Compd **1c** was prepared from the corresponding bromohydrin by the action of refluxing Et_2NH–benzene mixture (15 hr). An Et_2O soln of the base (obtained as above for **1b**) was treated with ethereal HCl, giving a hygroscopic brown dihydrochloride, which upon rapid recrystn from *i*-PrOH–Et_2O yielded 42% of analytically pure, hygroscopic monohydrochloride (**1c**), mp 135–138° dec.

Isatins.—The 6-Cl, 6-Br, 6-F, 6-CF_3, and 7-CF_3 isatins were prepd according to published procedures.[13] Mixtures of 4- and 6-substituted isatins were sepd by the method of Sadler.[18]

Quinoline-2,4-dicarboxylic acids (14) were prepared from the corresponding isatins by the method of Senear, *et al.*[14]

Cinchoninic acids (15) were obtained from the corresponding quinoline-2,4-dicarboxylic acids **14** by decarboxylation, in refluxing $PhNO_2$ for 1 hr, or in Ph_2O at 215° for 15 min.

α-(Bromomethyl) 7-Trifluoromethyl-4-quinolyl Ketone·HBr, (5e).—A stirred soln of 12.1 g (0.05 mole) of **15b** in 60 ml of $SOCl_2$ was refluxed for 1.5 hr. The $SOCl_2$ was distd at 1 atm pressure and 100 ml of dry C_6H_6 was added and distd. A soln of the residue in 125 ml of dry Et_2O was filtered through glass wool, stored in a dropping funnel under a $CaCl_2$ drying tube, and added dropwise over 0.5 hr to a cooled, stirred soln of 6 g (0.14 mole) of CH_2N_2 in 415 ml of Et_2O, a yellow ppt appearing toward the end. The mixture was stirred for 4 hr and then treated dropwise with 40 ml of 48% HBr. After 1 hr of additional stirring the tan solid **5e** was collected, washed with 30% AcOH–Et_2O, and oven-dried; 12.54 g (63%), yellow, mp 187–193° dec.

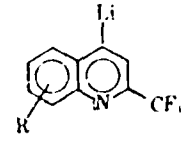
7-Trifluoromethyl-4-quinolylethylene Oxide (7a).—A soln of 9.36 g (0.024 mole) of **5e** in 75 ml of MeOH was treated with aq 5% $NaHCO_3$ until pH 7 was reached; it was then treated dropwise over 15 min with a soln of 1.5 g of $NaBH_4$ in 15 ml of H_2O to which had been added 4 ml of 2 *N* NaOH. After stirring for 1 hr, diluting with 125 ml of H_2O, and extg with petr ether (30–60°), the ext was dried (K_2CO_3) and evapd, giving 4.62 g (82%), wax product, mp 53–59°, recrystd from isooctane, 4.01 g (72%), mp 58–60°.

α-(Di-*n*-butylaminomethyl)-7-trifluoromethyl-4-quinolinemethanol Succinate (1d).—A stirred soln of **7a** (4.0 g, 0.0168 mole) and 20 ml of *n*-Bu_2NH was heated at 120° for 1.5 hr. After evapg excess *n*-Bu_2NH *in vacuo*, the residual oil was taken up in Et_2O; and the hydrochlorides were fractionally pptd by ethereal HCl. The first crop was crystn (*n*-Bu_2NH·HCl), but subsequent crops were gums from which Et_2O was decanted. Treatment of these with NaOH soln and extn with Et_2O, drying ($MgSO_4$), and retreating with ethereal HCl gave a tan oil which solidified upon cooling with Dry Ice–acetone; white, hygroscopic. Treatment of the salt with base and extn with Et_2O gave 3.51 g of tan oil (57%). A 125-ml Et_2O soln of this was treated with an equimolar amount (1.13 g) of succinic acid in 450 ml of EtOH. Evapn to 400 ml and standing at 0° for several days gave 3.61 g (44%) of **1d** succinate, mp 96–97.5°; a second crop of 0.60 g (7%) was obtained on concn of the Et_2O soln to 100 ml (total yield 51%).

2-Pyridyl 1-Trifluoromethyl-4-quinolyl Ketone (1b). A.—Treatment of **15b** (9.67 g, 0.01 mole) with 2-PyLi (0.189 mole) in 30% THF–Et_2O at −70° and crystn the product from EtOH yielded 5.85 g of tan solid, mp 105–165°, which was then sublimed (overnight) at 110° (0.05 mm); 1.90 g (16%), colorless; mp 117–119°.

(18) P. W. Sadler, *J. Org. Chem.*, **21**, 169 (1956).

TABLE II



R	Reactant[a]	Products[a]
6-Cl	PyCN	QCOPy (43%)
6-Me	PyCN	QCOPy (76%)
H	PyCHO	QCHOHPy (43%)
6-Me	PyCHO	QCHOHPy (29%)
6-Me	PipCOOH	QH (**23**, 55%)
6,8-Me_2, 6-Cl	PipCOOH	None isolated
6-Me	MeCN[b]	QH (**23**, 61%)
6-OMe, 6,8-Cl_2	MeCN[b]	None isolated
6-Me	Et_2NCH_2CN[b,c]	QH (**23**, 30%); QCH_2CN (**8a**, 30%, mp 104°);[d] QCH_2CONH_2 (**9a**, 20%, mp 200°);[e] **10** (25%)[f]
6-Cl	Et_2NCH_2CN[b]	QCH_2CONH_2 (**9b**, 50%)[g]

[a] Q = Substituted 4-quinolyl; Py = 2-pyridyl; Pip = 2-piperidyl. [b] Reaction time 4 hr. [c] Worked up by column chromatography on silica gel, eluting successively with petr ether (30–60°), C_6H_6, $CHCl_3$, and Me_2CO. [d] Ir (Nujol) 2248 cm^{-1} (C≡N). [e] *Anal.* $C_{13}H_{12}F_3N_3O$, N; ir (Nujol) cm^{-1}, 3350, 3195 (NH_2), 1675 (C=O). [f] Bp 120° (3 mm); *Anal.* $C_{12}H_{12}N_4$, C, H; N, calcd 25.00, found 24.43, ir (neat) 3480, 3360 (NH_2), 3970, 3940, 3830 (CH), 2175 (C≡N) and 1630 (C=C, C=N) cm^{-1}; nmr ($CDCl_3$) δ 0.97 (m, 12, CH_3), 2.48 (m, 8, CH_2), 3.26 (s, 2, NCH_2), and 5.26 (s, 2, NH_2). [g] Ir (KBr) 3350, 3165 (amide NH_2), 1680 cm^{-1} (amide C=O).

B.—Ethyl 7-trifluoromethylcinchoninate (8.3 g, 0.031 mole), when treated in Et_2O as above with 0.137 mole of 2-PyLi, gave 6.25 g (67%) of **11b**, mp 111–114°. No **17** was found.

2-Pyridyl 2-(2-Pyridyl)-7-trifluoromethyl-4-quinolyl Ketone (17).—*Recrystn from MeCN of the residue from the above sublimation of* **11b** yielded 1.87 g of **17** (12%), mp 169°–171°.

α-(2-Piperidyl)-8-trifluoromethyl-4-quinolinemethanol·HCl (2d).—A mixture of 5.0 g (0.0165 mole) of **11a**, 1.2 ml of concd HCl, 0.25 g of PtO_2, and 125 ml of abs EtOH was hydrogenated at 2.8 kg/cm² for 1 hr; total H_2 absorbed, 0.059 mole. Filtering, evapn to 30 ml, pouring into dil NaOH, Et_2O extn, drying ($MgSO_4$), treatment with ethereal HCl, decantation from the gummy salt, dissolving in abs EtOH, and treatment with anhyd Et_2O until cloudy gave an off-white ppt, which was filtered and air-dried: 0.80 g (14%), mp 165–172° dec; recrystd from *i*-PrOH–Et_2O; 0.22 g (4%); tan; mp 204–206° dec.

α-(2-Piperidyl)-8-trifluoromethyl-1,2,3,4-tetrahydro-4-quinolinemethanol (16).—A mixture of 9.50 g (0.0315 mole) of **11a**, 5 ml of concd HCl, 0.95 g of PtO_2, and 200 ml of abs EtOH was hydrogenated as above, absorbing 0.15 mole. The base was recrystd from a small vol of MeCN: 0.69 g; colorless; mp 179–183°.

α-(2-Piperidyl)-6- and -8-fluoro-2-trifluoromethyl-4-quinolinemethanol·HCl (2b and 2c) were prepared by the previously reported reaction sequence:[5] the 4-quinolone → QBr → QCOOH → QCOPy → **2b,c**.

α-(2-Piperidyl)-6-fluoro-2-*p*-tolyl-4-quinolinemethanol (2a) was obtained (by published procedure[5]) from the corresponding 6-fluoro-2-*p*-tolylcinchoninic acid (prepared by the Pfitzinger reaction between 5-fluoroisatin and *p*-methylacetophenone).

Reactions of 2-Trifluoromethyl-4-quinolyllithium Derivatives (Prepared as Previously Described[5]).—The products were identified by comparison of mp and ir spectra with those of authentic samples.[5] In a typical example, a slight excess of 2-cyanopyridine was added to a soln of 6-methyl-2-trifluoromethyl-4-quinolyllithium in dry Et_2O under N_2 at −70°. After 2 hr the mixture was warmed to room temp and hydrolyzed (H_2O). The resulting α-(2-pyridyl) 6-methyl-2-trifluoromethyl-4-quinolyl ketone was recrystd from EtOH (30%) mp 155° (lit.[5] mp 153°). The results of these experiments are shown in Table II.

As might have been expected the reaction between 4-quinolyllithiums and piperolenic acid which has two active hydrogens and would form a dianion with two proximate negative charges, failed to give the piperidyl ketone; in the case of the 6-Me derivative the corresponding parent quinoline was obtained in 55% yield.

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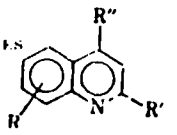
The reaction of 4-cyano-6,8-dimethyl-2-trifluoromethylquinoline (13[a]) with 2-PyLi in Et_2O at −70° for 1 hr under N_2 and purification by column chromatography on silica gel ($CHCl_3$) gave 50% of 2-pyridyl 6,8-dimethyl-2-trifluoromethyl-4-quinolyl ketone, mp 94° (lit.[a] mp 98°).

TABLE III

4-FUNCTIONALIZED SUBSTITUTED QUINOLINES

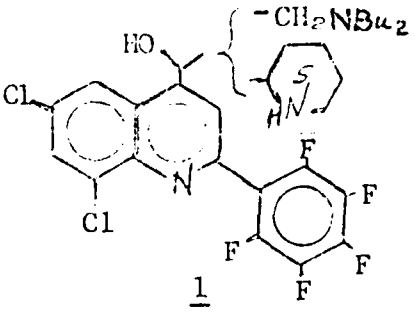


No.[a]	R	R'[b]	R''[c]	Mp, °C[d-g,p]	Yield, %	Analysis[q-z]
23	6-Me	CF_3	H	89		$C_{11}H_8F_3N$[r,s]
18a	6-F	CF_3	OH	255–260	74	$C_{10}H_5F_4NO$
18b	8-F	CF_3	OH	144–145	69	$C_{10}H_5F_4NO$
18c	6,8-F_2	CF_3	OH	164–165	63	$C_{10}H_4F_5NO$[s]
19a	6-F	CF_3	Br	93–95	78	$C_{10}H_4BrF_4N$
19b	8-F	CF_3	Br	68–69	94	$C_{10}H_4BrF_4N$
19c	6,8-F_2	CF_3	Br	84–85	96	$C_{10}H_3BrF_5N$
14a	8-CF_3	COOH	COOH	230–232 dec	92	$C_{12}H_6F_3NO_4$
14b	7-CF_3	COOH	COOH	235–237 dec	85	$C_{12}H_6F_3NO_4$
14c	7-F	COOH	COOH	240–242 dec	91	$C_{11}H_6FNO_4$
14d	7-Br	COOH	COOH		94	Not anal.
15a	8-CF_3	H	COOH	232–235 dec[e,A]	85	$C_{11}H_6F_3NO_2$
15b	7-CF_3	H	COOH	283–286 dec[e,A]	91	$C_{11}H_6F_3NO_2$
15c	7-F	H	COOH	289–290 dec[e]	35	$C_{10}H_6FNO_2$
15d	7-Br	H	COOH	247–250 dec[f]	86	$C_{10}H_6BrNO_2$
15e	6-F	PhMe	COOH	274–275	92	$C_{17}H_{12}FNO_2$
20a	6-F	CF_3	COOH	207–209	65	$C_{11}H_5F_4NO_2$
20b	8-F	CF_3	COOH	218–220	78	$C_{11}H_5F_4NO_2$
25	7-CF_3	H	COOEt	67–69[f]	91	Not anal.
26	6,8-Me_2	PhMe	COOMe	122–123	88	$C_{20}H_{19}NO_2$
27	6,8-Me_2	PhMe	COOEt	117–118	97	$C_{21}H_{21}NO_2$
4a	6,8-Me_2	PhMe	COCl	138–139[f]	67	$C_{19}H_{16}ClNO$
6a	6,8-Me_2	PhMe	COMe	123.5–124.5	72	$C_{20}H_{19}NO$
6b	6-Me	PhMe	COMe	117–118	86	$C_{19}H_{17}NO$
6c	6-Me	PhOMe	COMe	123–124	88	$C_{19}H_{17}NO_2$
6d	6-Me	PhF	COMe	116–118	68	$C_{18}H_{14}FNO$
6e	6-Me	PhCl	COMe	133–134	85	$C_{18}H_{14}ClNO$
6f	6,8-Me_2	PhOMe	COMe	101–102	81	$C_{20}H_{19}NO_2$
24	6,8-Me_2	PhCl	COEt	120–121	65	$C_{20}H_{18}ClNO$,
28	6,8-Me_2	PhMe	$COCHN_2$	159–160	78	$C_{20}H_{17}N_3O$
5a[w]	6,8-Me_2	PhMe	$COCH_2Br$	145–147	88	$C_{20}H_{18}BrNO$
5b	6-Me	PhMe	$COCH_2Br$	132–135	71	$C_{19}H_{16}BrNO$
5c	6-Me	PhOMe	$COCH_2Br$	106–108	75	$C_{19}H_{16}BrNO_2$
5d	6-Me	PhF	$COCH_2Br$	134–136	72	$C_{18}H_{13}BrFNO$
5e	7-CF_3	H	$COCH_2Br$	203–205 dec[x]	63	$C_{12}H_7BrF_3NO\cdot HBr$[t]
7a	7-CF_3	H	CH—CH_2 (O)	60–62[f]	72	$C_{12}H_8F_3NO$[r]
9a	6-Me	CF_3	CH_2CONH_2	200	20	$C_{13}H_{11}ClF_3N_3O$[r]
9b	6-Cl	CF_3	CH_2CONH_2	260–261	50	$C_{12}H_8ClF_3N_3O$[w]
21a	6-F	CF_3	COPy	121–122	90	$C_{16}H_8F_4N_2O$
21b	8-F	CF_3	COPy	130–132	62	$C_{16}H_8F_4N_2O$
21c	6-F	PhMe	COPy	172–174	49	$C_{22}H_{15}FN_2O$
11a	8-CF_3	H	COPy	141–141.5	76	$C_{16}H_9F_3N_2O$
11b	7-CF_3	H	COPy	118–119.5	16	$C_{16}H_9F_3N_2O$
17	7-CF_3	Py	COPy	170–172[m]	12	$C_{21}H_{12}F_3N_3O$
22a	6-F	CF_3	CHOHPy	123–128	97	$C_{16}H_{10}F_4N_2O$
22b	8-CF_3	H	CHOHPy	133–134	76	$C_{16}H_{11}F_3N_2O$
2a	6-F	PhMe	CHOHPip	165–168	33	$C_{22}H_{23}FN_2O$
2b	6-F	CF_3	CHOHPip	256–258 dec	73	$C_{16}H_{16}F_4N_2O\cdot HCl$
2c	8-F	CF_3	CHOHPip	275–278 dec	62	$C_{16}H_{16}F_4N_2O\cdot HCl$[s]
2d	8-CF_3	H	CHOHPip	204–206 dec[n]	4	$C_{16}H_{17}F_3N_2O\cdot HCl$[r]
16[o]	8-CF_3	H	CHOHPip	182–185[m]	6–46	$C_{16}H_{21}F_3N_2O$[r]
1a	6,8-Me_2	PhMe	$CHOHCH_2NEt_2$	217–219 dec[e]	92	$C_{24}H_{30}N_2O\cdot HCl$[r]
1b(·HCl)	6,8-Me_2	PhMe	$CHOHCH_2NBu_2\cdot HCl$	200–202[k]	93	$C_{28}H_{38}N_2O\cdot HCl$[r]
1b(base)			$CHOHCH_2NBu_2$	78–79[l]		$C_{28}H_{38}N_2O$
1c	7-Cl	H	$CHOHCH_2NEt_2$	135–138 dec[m]	42	$C_{17}H_{17}ClN_2O\cdot HCl$[r]
1d	7-CF_3	H	$CHOHCH_2NBu_2\cdot S$[c]	96–97[p]	51	$C_{23}H_{32}F_3N_3O_5$[r]

[a] 16 is the 1,2,3,4-tetrahydroquinoline. [b] Ph = phenyl substituent para; Py = 2-pyridyl; Pip = 2-piperidyl. [c] 1d: S = succinic acid. [d] dec = melts with decomposition. [e] Decarboxylation solvent, Ph_2O; [f] $PhNO_2$. [g] Recrystallization solvent, EtOH, unless otherwise specified as follows: [h] 2-methoxyethanol; [i] hexane; [j] AcOEt; [k] AcOH; [l] isooctane; [m] MeCN; [n] *i*-PrOH-Et_2O; [o] EtOH-Et_2O; [p] Me-CO-pentane. [q] Within ± 0.4%, and for C, H, except where otherwise specified: [r] for C, H, N. [s] for C, H, F; [t] for C, H, Br; [u] for N. [v] C: calcd 62.56, found 62.00. [w] C, H: calcd 49.91, 2.77, found, 49.32, 2.08. [x] C: calcd, 52.68 found, 53.29. [y] A. L. Crosby, M. S. Thesis, University of Virginia, Charlottesville, Va., 1950.

Experiments Toward 6,8-Dichloro-2-perfluorophenyl-4-quinoline Aminoalcohols of Type 1.

Synthetic efforts were frustrated by the facility of displacement of one F-atom and were discontinued. The yields of cinchophens 2 (and 3 by accompanying ethanolysis) were greatly improved by the modified Pfitzinger procedure. Reactions with 2-PyLi in Et_2O-THF or Et_2O gave 2-pyridyl ketone ***5*** and dipyridyl ketone ***6***.



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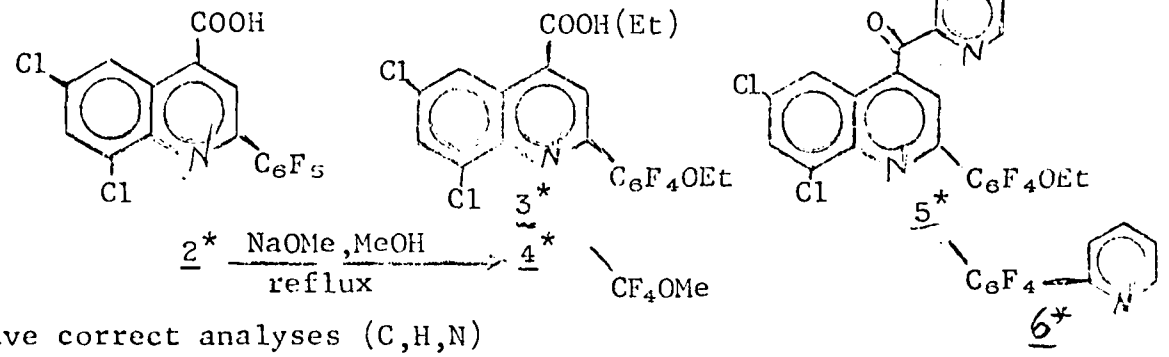

*gave correct analyses (C,H,N)

Antimalarials. II.[1a] α-(2-Piperidyl)- and α-(2-Pyridyl)-2-trifluoromethyl-4-quinolinemethanols[1b]

Journal of Medicinal Chemistry, 11, 267 (1968).

ROGER M. PINDER AND ALFRED BURGER

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

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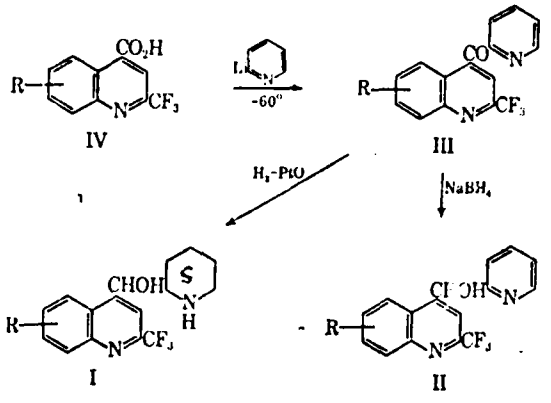
A series of α-(2-piperidyl)-2-trifluoromethyl-4-quinolinemethanols was synthesized in the hope that replacement of 2-aryl by 2-CF_3 would decrease the photosensitizing qualities of the 2-aryl analogs. All of the 2-trifluoromethyl derivatives carrying 6- or 8-CH_3, -CH_3O, or -Cl substituents increased the survival time of mice infected with *Plasmodium berghei*, but they retained photosensitizing properties, albeit less than the 2-aryl-substituted analogs.

A number of α-(2-piperidyl)-4-quinolinemethanols[1a,2,3] have high antiplasmodial activity in avian infections.[4] High activity is associated with a substituent in the 2 position of the quinoline nucleus, particularly phenyl, which will prevent oxidation at that position; the cinchona alkaloids and related compounds are rapidly biotransformed in man to the inactive carbostyril derivatives.[5] The most promising compound, 6,8-dichloro-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol, was eighty times more active than quinine against *Plasmodium cathemerium* in the duck,[4] but it produced severe photosensitivity and did not find clinical use in man.[6] There is renewed interest in this type of antimalarial, both because it is firmly bound to host tissues and slowly released and therefore has repository properties, and because it has shown one of the highest recorded activities against *Plasmodium berghei* in mice.[7] It has been theorized that phototoxicity arises because of the increased resonance conjugation from the 2-aryl group;[7] a trifluoromethyl group in lieu of a 2-aryl group may modify this property and still prevent oxidation to the carbostyril. We are therefore reporting the synthesis and antimalarial activity of a series of α-(2-piperidyl)-2-trifluoromethyl-4-quinolinemethanols (I) and of the corresponding α-(2-pyridyl) compounds (II) which represent a new type of analog.

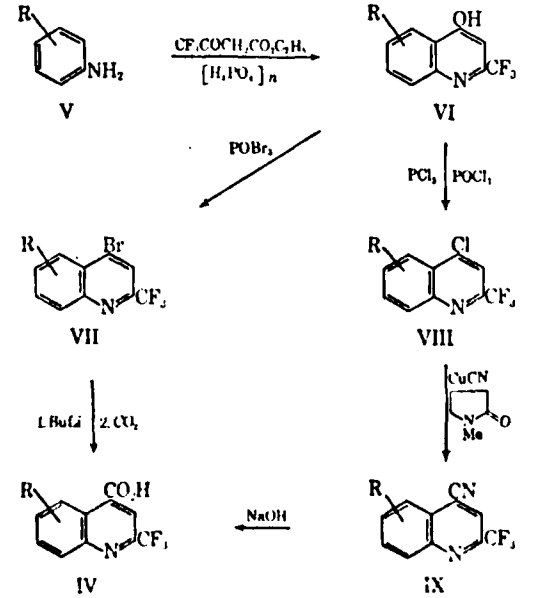
The synthetic approach to amino alcohols of types I and II, starting from the corresponding quinoline-4-carboxylic acids (IV), is outlined in Scheme I and reduces the number of steps from six[2,3] to two.[1a] Addition of 2-lithiopyridine to the acids at −60°, followed by hydrolysis, gave the pyridyl ketones (III). Catalytic hydrogenation of III selectively reduced the carbonyl group and the pyridine nucleus without attacking the qunoline nucleus, giving the amino alcohols of type I, while reduction with sodium borohydride gave amino alcohols of type II.

SCHEME I



The 2-trifluoromethylcinchoninic acids (IV) were prepared by the route outlined in Scheme II. Condensation of a substituted aniline (V) with ethyl 4,4,4-trifluoroacetoacetate[8] in the presence of polyphosphoric

SCHEME II



(1)(a) Paper I: D. W. Boykin, Jr., A. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 459 (1967). (b) This work was supported by the U. S. Army Medical Research and Development Command, Contract No. DA-49-193-MD-2355, Contribution No. 297, A. Burger and R. E. Lutz co-responsible investigators.

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(7) D. P. Jacobus, Abstracts, 154th National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, M8.

(8) J. Burdon and V. C. R. McLoughlan, *Tetrahedron*, **20**, 2163 (1964).

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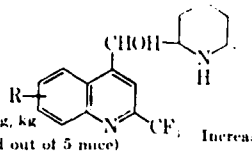
TABLE I

ANTIMALARIAL ACTIVITY OF α-(2-PIPERIDYL)-2-TRIFLUOROMETHYL-4-QUINOLINEMETHANOLS[a]



R	Dose, mg/kg (no. cured out of 5 mice)	Increase in mean survival time, days
6-OCH_3	80 (1)	...
	160 (1)	...
	320 (2)	...
	640 (4)	...
6-CH_3	160 (0)	7.1
	320 (0)	7.5
	640 (0)	8.5
8-CH_3	160 (0)	7.3
	320 (1)	...
	640 (5)	...
6,8-$(CH_3)_2$	160 (0)	8.3
	320 (2)	...
	640 (3)	...
6-Cl	160 (0)	7.5
	320 (0)	8.7
	640 (1)	...

[a] Tests were carried out in mice infected with *P. berghei*.[13] Test results were supplied by Walter Reed Army Institute of Research, Washington, D. C. Enhancement in survival time of treated animals is regarded as evidence of antimalarial activity. A compound is considered active if the mean survival time of the treated group is more than double the mean survival time (7.0 ± 0.5 days) of the control group; it is said to be curative when the animal survives up to 60 days.

acid gave only the 4-quinolinols (VI). This reaction with ethyl acetoacetate itself gives a mixture of the 2- and 4-quinolinols, depending upon whether the amine reacts with the ester or the β-keto group.[9] The electron-withdrawing power of the trifluoromethyl group apparently leads to exclusive reaction of the (now) electronegative β-keto group with the amine.[10] The 4-quinolinols were brominated[11] or chlorinated[10] with phosphorus oxybromide or oxychloride in excellent yields. The 4-bromoquinolines (VII) reacted readily with *n*-butyllithium at −35°, and treatment of the resulting lithioquinolines with dry CO_2 gave the required cinchoninic acids (IV). The 4-chloroquinolines (VIII) were converted to the corresponding nitriles by reaction with cuprous cyanide in N-methylpyrrolidone,[12] and the nitriles were then hydrolyzed to the cinchoninic acids.

Biological Data.—The antimalarial test[13] data for the α-(2-piperidyl)-2-trifluoromethyl-4-quinolinemethanols are listed in Table I. These compounds possessed moderate antimalarial activity but were photosensitizing. The unsubstituted α-2-piperidyl-2-trifluoromethyl-4-quinolinemethanol, however, was inactive. The corresponding α-(2-pyridyl) compounds were inactive, but did not cause photosensitization.

(9) R. C. Elderfield, "Heterocyclic Compounds," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 76.

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(12) M. S. Newman and H. Boden, *J. Org. Chem.*, **26**, 2525 (1961).

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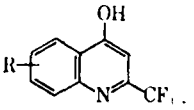
Experimental Section

Melting points were determined in a capillary melting point bath and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

In accordance with previous observations[13] regarding the properties of 2-trifluoromethylquinolines, the compounds described herein did not form salts due to the decreased basicity of the quinoline nitrogen atom. The 2-trifluoromethyl-4-quinolinols (Table II) and 2-trifluoromethyl-4-chloroquinolines (Table III) were prepared according to Dey and Joullié.[10]

TABLE II

2-TRIFLUOROMETHYL-4-QUINOLINOLS

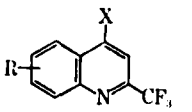


R	Yield, %	Mp, °C[a]	Formula[b]
6-Cl	70	274–275	$C_{10}H_5ClF_3NO$[c]
8-Cl	55	134–135	$C_{10}H_5ClF_3NO$
6,8-Cl_2	58	180–181	$C_{10}H_4Cl_2F_3NO$
6,8-$(CH_3)_2$	65	150–151	$C_{12}H_{10}F_3NO$

[a] Recrystallized from EtOH. [b] All compounds were analyzed for C, H, N. Their ir spectra were as expected. [c] N: calcd, 5.32; found, 5.82.

TABLE III

2-TRIFLUOROMETHYLQUINOLINE DERIVATIVES



R	X	Yield, %	Mp, °C[a]	Formula[b]
H	Br	80	38–39	$C_{10}H_5BrF_3N$
H	CN	63	130–131	$C_{11}H_5F_3N_2$[c]
6-CH_3	Br	91	70–71	$C_{11}H_7BrF_3N$
6,8-$(CH_3)_2$	Br	95	115–116	$C_{12}H_9BrF_3N$
6,8-$(CH_3)_2$	Cl	95	99–101	$C_{12}H_9ClF_3N$
6,8-$(CH_3)_2$	CN	76	126–127	$C_{12}H_9F_3N_2$
8-CH_3	CN	65	80–81	$C_{12}H_7F_3N_2$
6-Cl	Br	90	119–120	$C_{10}H_4BrClF_3N$
6-Cl	Cl	92	103–104.5	$C_{10}H_4Cl_2F_3N$[d]
6-Cl	CN	51	142–143	$C_{11}H_4ClF_3N_2$
8-Cl	Cl	84	58.5–59.5	$C_{10}H_4Cl_2F_3N$
8-Cl	CN	42	167–169	$C_{11}H_4ClF_3N$
6,8-Cl_2	Br	97	75–76	$C_{10}H_3BrCl_2F_3N$
6,8-Cl_2	Cl	88	75–76	$C_{10}H_3Cl_3F_3N$
6-OCH_3	Br	92	124–125	$C_{11}H_7BrF_3NO$

[a] Recrystallized from EtOH. [b] All compounds were analyzed for C, H, N. Their ir spectra were as expected. [c] N: calcd, 12.61; found, 12.20. [d] C: calcd, 45.13; found, 45.56.

2-Trifluoromethyl-4-bromoquinolines (Table III).—In a typical preparation, a mixture of 2-trifluoromethyl-4-quinolinol (30 g, 0.14 mole) and $POBr_3$ (57 g, 0.2 mole) was stirred at 140° for 3 hr. The warm mixture was poured into ice–water (600 ml), and the solid material was filtered off and recrystallized from EtOH, yield 31 g.

2-Trifluoromethylcinchoninic Acids (Table IV). A. In a typical example, a solution of 4-bromo-2-trifluoromethylquinoline (55 g, 0.2 mole) in dry ether (600 ml) was added over 15 min to an Et_2O solution of *n*-BuLi (prepared from 3.5 g of Li wire and 35 g, 0.25 mole, of *n*-BuBr), stirred under N_2 at −35° for 20 min, and was then poured, with vigorous stirring, onto powdered solid CO_2. After removal of ether, the residue was dissolved in H_2O and the acid precipitated by careful acidification with AcOH. The collected solid was recrystallized from EtOAc, yield 31 g.

B.—The 4-chloroquinolines were converted to the 4-cinchoninonitriles (Table III) by the method of Newman and Boden.[12] In a typical hydrolysis, a mixture of 8-methyl-2-

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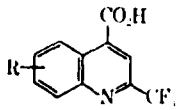
TABLE IV

2-TRIFLUOROMETHYLQUINOLINECARBOXYLIC ACIDS

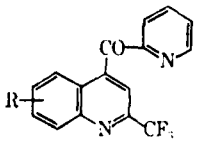


R	Method	Yield, %[a]	Mp, °C[b]	Formula[c]
H	A, B	65, 51	196–197	$C_{11}H_6F_3NO_2$
6-CH_3	A	67	215–216	$C_{12}H_8F_3NO_2$
8-CH_3	B	51	199–200	$C_{12}H_8F_3NO_2$
6,8-$(CH_3)_2$	A, B	62, 65	224–226	$C_{13}H_{10}F_3NO_2$
6-Cl	A, B	72, 74	226–227	$C_{11}H_5ClF_3NO_2$[d]
8-Cl	B	18	210–212	$C_{11}H_5ClF_3NO_2$[e]
6-OCH_3	A	63	238–239	$C_{12}H_8F_3NO_3$

[a] Yield from sequence B is based on the starting 4-chloroquinolines. [b] Recrystallized from EtOAc. [c] See footnote *b*, Table III. [d] C: calcd, 47.93; found, 47.36. [e] No N analysis.

TABLE V

2-TRIFLUOROMETHYL-4-PYRIDOYLQUINOLINES



R	Yield, %	Mp, °C[a]	Formula	Analyses
H	63	130–132	$C_{16}H_9F_3N_2O$	C, H, N
6-CH_3	60	125–126	$C_{17}H_{11}F_3N_2O$	C, H
8-CH_3	64	98–99	$C_{17}H_{11}F_3N_2O$	C, H, N
6,8-$(CH_3)_2$	73	119–120	$C_{18}H_{13}F_3N_2O$	C, H
6-Cl	48	152–153	$C_{16}H_8ClF_3N_2O$	C, H
8-Cl	31	116–117	$C_{16}H_8ClF_3N_2O$	C, H
6,8-Cl_2	34	138–139	$C_{16}H_7Cl_2F_3N_2O$	C, H, N
6-OCH_3	67	132–133	$C_{17}H_{11}F_3N_2O_2$	C, H, N

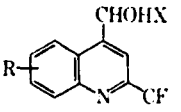
[a] Recrystallized from EtOH.

trifluoromethylcinchoninonitrile (23.6 g, 0.1 mole) and a solution of NaOH (12 g, 0.3 mole) in H_2O (50 ml) and EtOH (120 ml) was stirred under reflux for 12 hr. The solution was evaporated to dryness, and the residue was dissolved in H_2O and filtered through Celite. The clear filtrate was acidified by dropwise addition of AcOH, and the white precipitate was collected and recrystallized from EtOAc, yield 20 g.

2-Pyridyl 4-Quinolyl Ketones (Table V).—To an ethereal solution of *n*-butyllithium (0.05 mole) at −60° was added rapidly 2-bromopyridine (8 g, 0.05 mole), and the brown mixture was stirred at −60° for 1 hr. Finely powdered 6-methoxy-2-trifluoromethylcinchoninic acid (5.4 g, 0.02 mole) was added all at once and the mixture was stirred at −60° for 2 hr. It was allowed to warm to room temperature and then hydrolyzed by addition of H_2O. The ether layer was dried ($MgSO_4$) and distilled to give a yellow solid, which was recrystallized from EtOH as yellow needles, yield 4.7 g.

TABLE VI

2-TRIFLUOROMETHYLQUINOLINE-4-METHANOL DERIVATIVES



R	X[a]	Yield, %	Mp, °C	Recrystn solvent	Formula[b]
H	Pip	50	254–255	EtOH	$C_{16}H_{19}F_3N_2O \cdot HCl$
H	Pyr	80	115–116	MeOH	$C_{16}H_{11}F_3N_2O$
6-CH_3	Pip	66	254–256	EtOH	$C_{17}H_{19}F_3N_2O \cdot HCl$
6-CH_3	Pyr	91	139–140	EtOH	$C_{17}H_{13}F_3N_2O$
8-CH_3	Pip	60	284–286	EtOH	$C_{17}H_{19}F_3N_2O \cdot HCl$
8-CH_3	Pyr	100	120–122	MeOH–C_6H_6	$C_{17}H_{13}F_3N_2O$
6,8-$(CH_3)_2$	Pip	55	279–280	EtOH	$C_{18}H_{21}F_3N_2O \cdot HCl$
6,8-$(CH_3)_2$	Pyr	86	128–129	MeOH–C_6H_6	$C_{18}H_{15}F_3N_2O$
6-Cl	Pip	45	265–266	EtOH	$C_{16}H_{18}ClF_3N_2O \cdot HCl$
6-Cl	Pyr	89	149–150	EtOH–petr ether[d]	$C_{16}H_{10}ClF_3N_2O$
8-Cl	Pip	28	248–250	EtOH	$C_{16}H_{18}ClF_3N_2O \cdot HCl$[c]
8-Cl	Pyr	78	124–125	MeOH–C_6H_6	$C_{16}H_{10}ClF_3N_2O$
6,8-Cl_2	Pip	33	262–264	EtOH	$C_{16}H_{17}Cl_2F_3N_2O \cdot HCl$
6,8-Cl_2	Pyr	82	138–139	EtOH–petr ether[d]	$C_{16}H_9Cl_2F_3N_2O$
6-OCH_3	Pip	52	241–242	EtOH	$C_{17}H_{19}F_3N_2O_2 \cdot HCl$
6-OCH_3	Pyr	100	172–173	MeOH	$C_{17}H_{13}F_3N_2O_2$

[a] Pip = 2-piperidyl; Pyr = 2-pyridyl. [b] See footnote *b*, Table III. [c] N: calcd, 7.35; found, 7.80. [d] Bp 30–60°.

α-(2-Piperidyl)-2-trifluoromethyl-4-quinolinemethanols (Table VI).—A solution of 6-methoxy-2-trifluoromethyl-4-quinolyl 2-pyridyl ketone (4 g) in EtOH (300 ml) containing 1 molar equiv of HCl was shaken with PtO_2 (200 mg) at 2.8 kg/cm² under H_2. The reduction was stopped when 4 equiv of H_2 had been absorbed; the catalyst was filtered off, and the residue was concentrated until crystallization began. Recrystallization from EtOH gave white needles, yield 2.2 g.

α-(2-Pyridyl)-2-trifluoromethyl-4-quinolinemethanols (Table VI).—$NaBH_4$ (0.26 g, 0.007 mole) was added portionwise to a stirred solution of 6-methoxy-2-trifluoromethyl-4-quinolyl 2-pyridyl ketone (2.2 g, 0.007 mole) in MeOH (200 ml), and the mixture was stirred at room temperature for 2 hr. MeOH was removed under reduced pressure and the residue was taken up in ether, washed (H_2O), and dried ($MgSO_4$). The ether was distilled, and the residue was recrystallized from MeOH, yield 2.3 g.

Acknowledgment.—This study has profited from frequent and helpful discussions with Professor R. E. Lutz and Drs. D. W. Boykin, Jr., and A. R. Patel of the University of Virginia.

Antimalarials. 7. Bis(trifluoromethyl)-α-(2-piperidyl)-4-quinolinemethanols[1]

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C. J. Ohnmacht,[2] A. R. Patel,[2] and R. E. Lutz*

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

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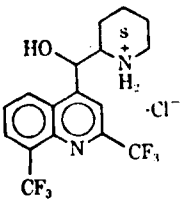
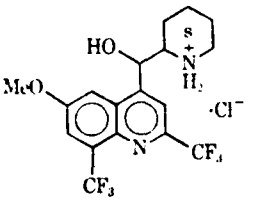
The 2,6-, 2,7-, and 2,8-bis(trifluoromethyl)-α-(2-piperidyl)quinolinemethanols, and the 6-methoxy derivative of the latter, have been synthesized from the appropriate 4-quinolones, through the 4-bromoquinolines, CO_2 carboxylations of the 4-Li derivatives, additions of 2-PyrLi, and H_2/Pt reductions of the resulting pyridyl ketones. An attempt to obtain the 2,5-bis(trifluoromethyl) analog utilized the corresponding 4-quinolone formed as a by-product in the synthesis of the 2,7 isomer; addition of the 4-Li derivative to 2-pyridaldehyde gave the α-pyridylmethanol, but subsequent H_2/Pt reduction of this gave only the 4-dihydroquinolone-α-(2-piperidyl)methanol.

The α-(2-piperidyl)-2-trifluoromethyl-4-quinolinemethanols carrying OCH_3, CH_3, or Cl in positions 6 or 8 have consistently shown only moderate or slight antimalarial activities against *Plasmodium berghei* in mice, and they were also moderately phototoxic.[3a] The synthesis of the 2,8-bis(trifluoromethyl) analog, **1**, begun before decision had been made to terminate work in this series, was nevertheless completed[1c] for comparison with the 9-phenanthrene amino alcohols where 3,6-disubstitution of CF_3 groups had brought a very considerable increase in antimalarial activity.[4] When this compd **1** proved to be curative at 20 mg/kg[1d,5] and relatively nonphototoxic,[1d,6] the synthesis of the 2,7 and 2,6 analogs **3** and **4** were undertaken to initiate evaluation of the pharmacological effects of different nuclear positions of 2 or more CF_3 groups with or without additional substituents.



1



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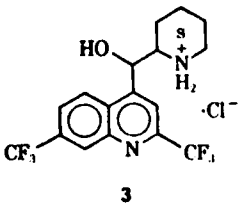

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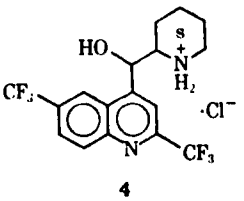

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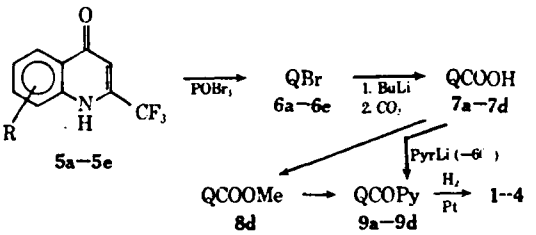
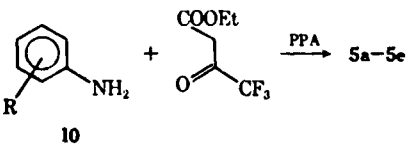
Four target drugs **1**–**4** were synthesized each in 4 steps from the corresponding 4-quinolones **5a**–**5d** by adaptations of known procedures,[3,7] as follows. Conversion by $POBr_3$ into the 4-bromoquinolines **6a**–**6d** and CO_2 carboxylation of the 4-Li derivative gave cinchoninic acids **7a**–**7d**. Addition of 2-PyrLi gave the pyridyl ketones **9a**–**9d**, but only **9a**,**b** were obtained in good yields; **9d** was best obtained through the ester **8d**. Reductions with H_2/Pt gave good yields of **1** and **2**, but mediocre yields of **3** and **4**.



Q = substituted 4-quinolyl; Pyr = 2-pyridyl; **a**, R = 8-CF_3; **b**, R = 8-CF_3-6-OMe; **c** R = 7-CF_3; **d**, R = 6-CF_3; **e**, R = 5-CF_3

The 4-quinolones **5a**–**5e** were obtained by PPA condensation of the appropriate trifluoromethylaniline (**10**) and ethyl 4,4,4-trifluoroacetoacetate in adaptation of previously described procedures.[3a,7] However, 3-trifluoromethylaniline gave a mixture of 2,7- and 2,5-bis-



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(trifluoromethyl)quinolones, **5c** and **5e**; this was best converted directly to a mixture of the 4-bromo derivatives, at which point it was separated into **6c** and **6e**.

The addition of 2-PyrLi to 2,6-bis(trifluoromethyl)-choninic acid (**7d**) gave, besides 27% of the pyridyl ketone **9d**, a 6% yield of a second product to which the structure **11** is assigned on the basis of anal. and ir, nmr, and mass spectra. The latter indicated formation of a fragment of relative intensity 100 corresponding to loss of Bu, and another of 32 corresponding to loss of Pyr.

The formation of **11** is reasonably interpreted in terms of reversible Michael addition of 2-PyrLi to the Li carboxylate of **7d** to give dianion **12**, subsequent loss of CO_2 giving the new dianion **13**, followed by C-alkylation by BuBr present in the reagent to give the monoanion of **11**. It may be significant that in the PyrLi reaction with ester **8d**, **11** was not detected as a product; and the pyridyl ketone **9d** was obtained in 55% yield.

In utilizing the limited amount of 2,5-bis(trifluoromethyl)-4-quinolone (**5e**), produced in the synthesis

(1) (a) This work was supported by the U. S. Army Medical Research and Development Command, Office of the Surgeon General, Contract No. DA-48-193-MD-2955, R. E. Lutz, Responsible Investigator. (b) Contribution No. 927 of the Army Research Program on Malaria. (c) Presented in part at the Southeast Regional American Chemical Society Meeting, Richmond, Va., Nov 1969, Abstract 255. (d) Antimalarial test results were supplied by the Walter Reed Army Institute of Research.

(2) Postdoctoral Research Associates.

(3) (a) R. M. Parker and V. Boekelheide, *J. Med. Chem.*, **11**, 267 (1968); (b) A. R. Patel, C. J. Ohnmacht, D. P. Gilbert, A. H. Crosby, and R. E. Lutz, *ibid.*, **14**, 198 (1971); (c) D. W. Boykin, A. R. Patel, and R. E. Lutz, *ibid.*, **11**, 273 (1968).

(4) E. A. Nodiff, *et al.*, in preparation.

(5) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(6) W. E. Rothe and D. P. Jacobus, *ibid.*, **11**, 366 (1968).

(7) A. S. Dey and M. M. Joullié, *J. Heterocycl. Chem.*, **2**, 113 (1965).

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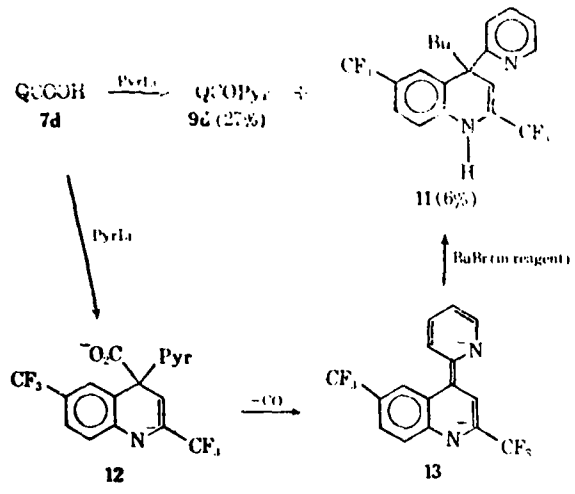
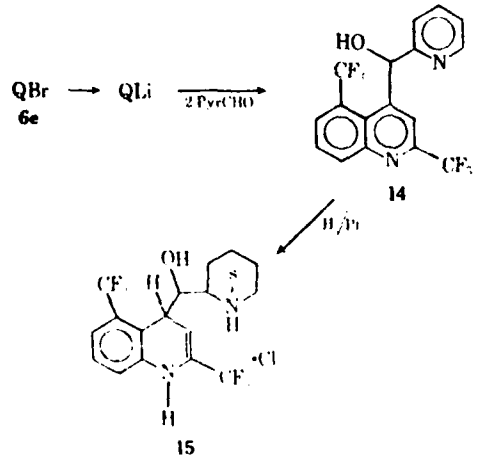


of the isomers from 3-trifluoromethylaniline, it was feared that the PyrLi addition might be impeded by steric effects of the 5 substituent. Consequently this quinolone was converted through the 4-bromoquinoline **6e** to the Li derivative which was added successfully to 2-pyridaldehyde, giving the pyridyl alcohol **14** (37%) after tedious chromatographic work-up. Unfortunately, catalytic hydrogenation of this gave the dihydroquinoline which is presumed to be α-(2-piperidyl)-2,5-bis(trifluoromethyl)-1,4-dihydro-4-quinolinemethanol·HCl (**15**; nmr: 4 H, exchangeable by D_2O). Possibly this overreduction was facilitated by the appreciable release of steric strain in the quinoline 4,5-group nonbonded interaction which, conversely, would in some degree oppose the otherwise facile oxidation of the dihydroquinoline to the quinoline.

It is noteworthy that all of the reductions, of the four 2-pyridyl ketones **9a**–**9d** and also the 2-pyridylmethanol **14**, were in the main stereospecific, giving in each case as the isolated pure product one only of the theoretically possible diastereoisomers (racemates). It is hoped that the stereoisomer of **1** will be isolated in the large scale synthesis now under way,[8] and that ir and nmr study will lead to configurational and conformational assignments, both here and, by analogy, in other cases where only one form has been obtained.



Biological Activities.[9] Antimalarial tests[9d,5] (Table I) showed target compounds **1**–**4** to be curative against

(8) E. J. Hanus, Arapet Subsl Preparation Co., work in progress.

TABLE I[a]

ANTIMALARIAL ACTIVITIES[a] AGAINST *P. berghei* IN MICE

	Antimalarial act., Dose, mg/kg				
Compd	10	20	40	80	160
1[c]	12.5[b]	4 C[b]	5 C		
2[d]	11.5	1 C	2 C	5 C	
3	1.9	10.9	3 C	5 C	
4	0.7	7.7	14.3	2 C	5 C

[a] Expressed as increases in mean survival times, in days, and [b] numbers of cures [C = cures], in 5 mice. A compd is considered to be active if the mean survival time of the treated group is more than double that of the control group (7.0 ± 0.5 days); and it is said to be curative when the animal survives up to 6 days. [c] Also active at 120 mg/kg against *P. gallinaceum* in chicks.[3d,5] [d] The corresponding 2-pyridyl ketone was inactive at 640 mg/kg. [e] See ref 1d and ref 5.

P. berghei in mice at 160 mg/kg or lower, and to compare very favorably with the 3,6-disubstituted 9-phenanthrene amino alcohols.[4] Furthermore, the phototoxicities of these compds were relatively low.[1d,6] The most active of these, the 2,8-bis(trifluoromethyl) compd, **1**, which was curative at 20 mg/kg, has now been prepared on a large scale[8] and is being evaluated further with promising results.

The one dihydroquinoline α-(2-piperidyl)methanol (**15**) with 2,5-bis(trifluoromethyl) groups obtained, proved to be inactive toward *P. berghei* in mice.[1d,5]

Because of the suspicion formerly held[6,9] that there might be a relation between phototoxicity and uv absorptivities, these values have been assembled in Table II.

TABLE II

UV ABSORPTIVITIES OF AMINO ALCOHOLS **1**–**4** IN MeOH

Uv absorptivities, Compd							
1		2		3		4	
nm	ϵ^{-3}	nm	ϵ^{-3}	nm	ϵ^{-3}	nm	ϵ^{-3}
222	46.7	236	52.5	226	46.0	225	42.1
283	6.6	284	5.8	281	5.4	279	5.8
304	4.0	294	5.3	304[a]	3.0	309	3.2
318	3.1	326	7.4	318	1.6	322.5	3.1
		338	8.5				

[a] Shoulder.

Experimental Results[10]

5-Methoxy-2-nitrobenzotrifluoride, mp 30–32° (lit.,[11] mp 39°), was prepd in 89% yield by refluxing a soln of 5-chloro-2-nitrobenzotrifluoride in KOH–MeOH soln (4 hr).[11]

5-Methoxy-2-aminobenzotrifluoride (10b) was prepd by hydrogenation of the above nitro compd (43.25 g, 0.195 mole) with 10% Pd/C (0.15 g) in 200 ml of MeOH (5 hr). The yield of distd product was 33.2 g (89%), bp 97–98° (9 mm). The hydrochloride was recrystd from EtOH: mp 229–231° dec. *Anal.* ($C_8H_8ClF_3NO$) C, H, N.

Quinolones 5a–**5e, bromoquinolines 6a**–**6e, cinchoninic acids 7a**–**7d, pyridyl ketones 9a**–**9d,** and **8**-(2-pyperidyl) **methanols 1**–**4,** and **15** were prepd by adaptations of previously described procedures.[1d,3] Specific minor variances are listed in Table III and in the following paragraphs.

(9) E. R. Atkinson and V. J. Puttock, **13**, 547 (1970), and refs cited.

(10) Satisfactory spectra were obtained where required for structural determination and randomly in other cases. Instruments used were Thomas Hoover apparatus for mp, ir Perkin-Elmer 337, nmr Hitachi P-L R-20, mass spectrograph Hitachi P-L RMU 6L. Microanalyses (Galbraith Lab Inc.) were correct within ±0.4%.

(11) F. H. Brown, C. W. Suckling, and W. B. Whalley, *J. Chem. Soc.*, 865 (1949).

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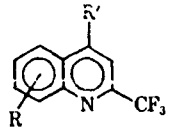
TABLE III

2-TRIFLUOROMETHYL-4-QUINOLINE DERIVATIVES[a]



Compd	R	R′	Mp, °C	% yield	Analysis[n]
5a[d,e]	8-CF_3	OH	128–132	75[k]	$C_{11}H_5F_6NO^q$
5b[d,f]	6-OMe-8-CF_3	OH	172–174	31	$C_{12}H_7F_6NO_2$
5c[b,c]	7-CF_3	OH	289–290	*l*	$C_{11}H_5F_6NO^q$
5d[c,d]	6-CF_3	OH	279–283	70	$C_{11}H_5F_6NO^q$
5e[c,b]	5-CF_3	OH	319–321 dec	*l*	$C_{11}H_5F_6NO^q$
6a[b,d]	8-CF_3	Br	62–64	95	$C_{11}H_4BrF_6N^q$
6b[b,d]	6-OMe-8-CF_3	Br	164–166	91	$C_{12}H_6BrF_6NO$
6c[b,d]	7-CF_3	Br	106–108	67[m]	$C_{11}H_4BrF_6N^q$
6d[d]	6-CF_3	Br	73–75	77	$C_{11}H_4BrF_6N^q$
6e[d,g]	5-CF_3	Br	49–51	18[m]	$C_{11}H_4BrF_6N^q$
7a[h]	8-CF_3	COOH	228–230.5	86	$C_{12}H_5F_6NO_2^q$
7b[d,h]	6-OMe-8-CF_3	COOH	246–248	57	$C_{13}H_7F_6NO_3$
7c[h]	7-CF_3	COOH	199–200.5	90	$C_{12}H_5F_6NO_2^q$
7d[h]	6-CF_3	COOH	216–218	87	$C_{12}H_5F_6NO_2^q$
8d[d,i]	6-CF_3	COOMe	130–131.5	100	$C_{13}H_7F_6NO_2^q$
9a[b,d]	8-CF_3	COPyr	128–129.5	61	$C_{17}H_8F_6N_2O$
9b[b,d]	6-OMe-8-CF_3	COPyr	164–165	90	$C_{18}H_{10}F_6N_2O_2$
9c[b,d]	7-CF_3	COPyr	124.5–125.5	27	$C_{17}H_8F_6N_2O^q$
9d[b,e]	6-CF_3	COPyr	138.5–140	13[n], 55[o]	$C_{17}H_8F_6N_2O^q$
14[d,e]	5-CF_3	CHOHPyr	107–109	37	$C_{17}H_{10}F_6N_2O$
1[c]	8-CF_3	CHOHPip·HCl	259–260 dec	53	$C_{17}H_{17}ClF_6N_2O$
2[b]	6-OMe-8-CF_3	CHOHPip·HCl	298–300 dec	86	$C_{18}H_{19}ClF_6N_2O_2$
3[b]	7-CF_3	CHOHPip·HCl	244–245 dec	24	$C_{17}H_{17}ClF_6N_2O$
4[c]	6-CF_3	CHOHPip·HCl	197–199 dec	22	$C_{17}H_{17}ClF_6N_2O$
1,4-Dihydroquinolines					
15[j]	5-CF_3	H, CHOHPip·HCl	193 dec[r]	27	$C_{17}H_{17}ClF_6N_2O$
11[b]	6-CF_3	Pyr, Bu	170–171	6	$C_{20}H_{18}F_6N_2$

[a] Pyr = 2-pyridyl; Pip = piperidyl. Recrystn solvent, or other purification methods are indicated: [b] *EtOH*. [c] *MeCN*. [d] *Sublimed*. [e] Hexane. [f] C_6H_6. [g] Column chromatog. [h] PhMe. [i] MeOH. [j] Me_2CO. [k] Yield of crude reaction product which was used directly in the next step. [l] Could not be fully sepd; total yield of mixt after crystn from EtOH, 70%. [m] Yield of pure material from a mixt of **5c** and **5e**. [n] Yield from the acid **7d**. [o] Yield from the ester **8d**. [p] Anal. were within ±0.3% for C, H, N or [q] for C, H. [r] nm 227, 242, 354 (ϵ^{-3} 2.14, 6.0, 3.1).

6-Methoxy-2,8-bis(trifluoromethyl)-4-quinolone (5b) was purified by recrystn from C_6H_6 rather than the often less effective soln in base and pptn by acid.[4,5]

2,5- and 2,7-Bis(trifluoromethyl)-4-bromoquinolines (6e,c.) A mixture of 2,5- and 2,7-bis(trifluoromethyl)-4-quinolones (39.2 g, 0.14 mole; recrystd from EtOH), and $POBr_3$ (57 g, 0.2 mole), was stirred at 140° for 3 hr and poured into ice H_2O. The product was extd with CH_2Cl_2 and recrystd from EtOH, giving pure **6c** (30.17 g, 63%), mp 104–106°. The residue obtd upon evapn of the EtOH liquors (15.13 g, 32%), was chromatogd on a 5-cm column of 1 kg of Woelm neutral alumina (activity no. 1). Eluting with hexane and 1, 2, 5, and 10% benzene–hexane gave 1.84 g of addnl **6c** (total yield 67%), 8.79 g (18%) of **6e**, mp 47–50°, and a small quantity of a mixt of these.

6-Methoxy-2,8-bis(trifluoromethyl)cinchoninic Acid (7b). The required 4-Li derivative was prepd by addn of the very slightly Et_2O-sol 4-Br deriv **6b** to a slight excess of *BuLi* in anhyd Et_2O and stirring for 2.5 hr. Pouring the reaction mixt onto dry powdered CO_2 gave **7b** (57%), mp 246–248°. A decrease in the prepn time of the Li compd led to a decrease in the yield of **7b** and a corresponding increase in recovered **6b**.

Methyl 2,6-bis(trifluoromethyl)cinchoninate (8d) was prepd in quant yield by 15-min refluxing of a MeOH soln of crude acid chloride which had been prepd by the reaction of **7d** with $SOCl_2$ (2 hr).

α-(2-Pyridyl)-2,6- and -2,7-bis(trifluoromethyl)-4-quinolyl ketones (9c,d) were isolated by column chromatog (Florisil, $CHCl_3$ as eluent) and recrystd from EtOH. Concn of recrystn liquors from **9d** yielded **11** (6%), pale yellow: ir (KBr) 3175 cm^{-1} (NH); nmr ($CDCl_3$–DMSO-d_6): δ 9.00 (s, 1, NH), 8.60 (m, 1), 7.61 (m, 1), 7.12 (m, 5), 5.00 (s, 1, H-3), 2.2 (m, 2), 0.95 (m, 7); mass spec (70 eV) *m/e* (rel intensity) 400 (2), 381 (5), 343 (100), 322 (32), 303 (4), 273 (16), 78 (20).

α-(2-Pyridyl)-2,5-bis(trifluoromethyl)-4-quinolinemethanol (14). A soln of 6.4 g (0.06 mole) of 2-pyridaldehyde in 40 ml of anhyd Et_2O was added dropwise at −70° under N_2 to a stirred Et_2O soln (150 ml) of 2,5-bis(trifluoromethyl)-4-quinolyllithium [from 7.93 g (0.023 mole) of **6e** and 17.2 g (0.05 mole) of 22% *BuLi* in hexane soln], with stirring for an addnl 2 hr. After hydrolysis the Et_2O layer was evapd to dryness, and the residue was chromatogd on 400 g of Florisil (C_6H_6 as eluent). The crude oil obtd was recryst from hexane, 3.64 g of **14** (tan), mp 95–103°. Sublimation at 70° (0.05 mm) returned 3.19 g (37%), mp 102–107°.

The Bis(trifluoromethyl)-α-(2-piperidyl)-4-quinolinemethanols (1–4) and the 5-Trifluoromethyl-1,4-dihydro Derivative (15). The catalytic hydrogenations of **9a**–**9d** and of **14** were carried out by published procedure in EtOH with PtO_2.[4] After filtration through Celite, the EtOH was vacuum evapd. Crude **3** and **4** were mutually purified by trituration of the residue with Et_2O and filtration.

Antimalarials. 3. α-Dibutylaminomethyl- and α-(2-Piperidyl)-3-quinolinemethanols[1]

Journal of Medicinal Chemistry, 14, 17 (1971)

CYRUS J. OHNMACHT, JR.,[2a] FREDDY DAVIS,[2b] AND ROBERT E. LUTZ*

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

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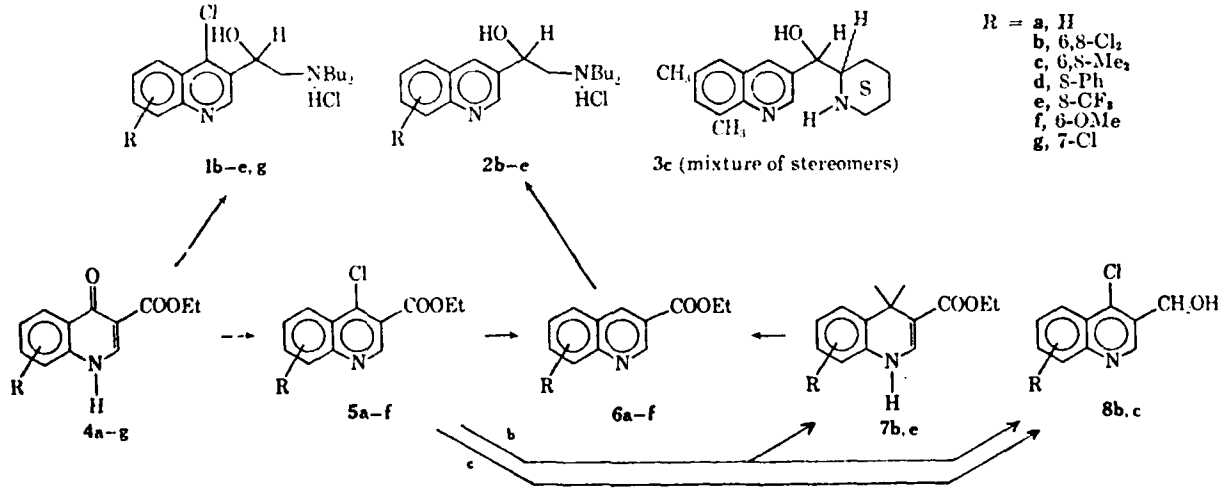
Eight α-dialkylaminomethyl-3-quinolinemethanols without 2 substituents were synthesized from 4-quinolone-3-carboxylic esters, by conversions into the 4-chloro esters and reductive 4-dechlorinations, and thence through the acids, diazomethyl ketones, and epoxides. Attempts to prepare α-(2-piperidyl) analogs involved complications due to nuclear additions of 2-pyridyllithium and nonselectivity in hydrogenations of the pyridyl ketones. One example, α-(2-piperidyl)-6,8-dimethyl-3-quinolinemethanol, fortuitously, was produced by Pt-H_2 on 4-chloro-6,8-dimethyl-3-quinolyl 2-pyridyl ketone (a diasteroisomeric mixture). These 3-amino alcohols were inactive against *Plasmodium berghei* in mice.

In continuation of the search for improved antimalarials, eight new α-aminoalkyl-3-quinolinemethanols without 2 substitutents,[1b] **1–3**, have been synthesized under the program of moving the amino alcohol group away from the 4 location in quinine and its many synthetic analogs. The hope was to find active drugs with a minimum of the phototoxicity so common to the 2-aryl-4-amino alcohols. As features of possible significance, these compounds lack the quasiconjugation of the amino alcohol group with the quinoline nuclear C=N–C system which is involved in the 4-quinoline amino alcohol series, and they have two rather than three nuclear carbons intervening between the quinoline N and the amino alcohol group.



The starting materials for these synthesis were the 4-quinolone-3-carboxylic esters **4a–g** which were easily obtainable by condensation of the appropriate aniline with ethoxymethylenemalonate ester.[3] Six 4-chloro esters **5a–f** were made from these by the action of $POCl_3$.

Reductive 4-dechlorinations of **5** to **6** were accomplished by variations of previously reported hydrogenolyses, using Pd–C[4] or Raney Ni[5] as catalyst. In four cases, **5a**, **c**, **d**, and **f**, the dechlorinations proceeded well using 10% Pd–C in glacial AcOH at 50°. However, **5e** under these conditions gave low and nonreproducible yields of **6e** along with an overreduction product, the 1,4-dihydroquinoline **7e**; and when the Pd–C reduction was carried out in ethanolic KOH at 50° the dihydroquinoline **7e** became the chief product (61%). This dihydro compound **7e** in a second step underwent S dehydrogenation in good yield to the desired 3-carbethoxyquinoline **6e**.

Attempted Pd–C and Raney Ni 4-monodehalogenation of the 4,6,8-trichloro derivative **5b** was unsuccessful. However, $NaBH_4$ reduction of **5b** in cold 2-methoxyethanol gave the dihydro-4-dehalogenated ester **7b** (39%) along with 4,6,8-trichloro-3-quinolinemethanol (**8b**), a result consistent with published observations.[4,6]

* To whom correspondence should be addressed.

(1) (a) Supported by U. S. Army Medical Research and Development Command, Contract No. DA-49-193-MD-2955. (b) Contribution No. 855 to the Army Research Medical Program on Malaria, R. E. Lutz, Responsible Investigator. (c) Work reported at the Southeast Regional American Chemical Society Meeting, Richmond, Va., Nov 1969, abstract 240. (d) An independent and parallel program of synthesis of six α-dialkylaminomethyl-2-(*o*-chlorophenyl)-4-quinolinemethanols has been completed under Contract No. DADA-17-67-C-7054 with Monsanto Research Corp., Boston, Mass., P. F. Donovan and W. R. Smith, "Synthesis of Quinolinemethanol Antimalarial Drugs", Final Report, May 1969; Annual Progress Report, Feb 1969. For comparison, and with permission of WRAIR and the Monsanto Research Corp., the 6 amino alcohols are listed in Table VII; experimental details are to be found in the reports cited.

(2) (a) Postdoctoral Research Assistant; (b) M. S. Thesis, University of Virginia, 1969; (c) preliminary work toward starting materials was done by D. P. Clifford and A. R. Patel, Postdoctoral Research Assistants.

(3) (a) C. C. Price and R. M. Roberts, *J. Amer. Chem. Soc.*, **68**, 1204 (1946). (b) J. H. Wilkinson, *J. Chem. Soc.*, 164 (1950). (c) R. Riegel, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1264 (1946).

(4) C. E. Kaslow and W. R. Clark, *J. Org. Chem.* **18**, 550 (1953).

(5) (a) R. E. Lutz, G. Ashburn, and R. J. Rowlett, Jr., *J. Amer. Chem. Soc.*, **68**, 1022 (1946); (b) V. S. Das and M. M. Joullié, *J. Heterocycl. Chem.*, **2**, 113 (1965); (c) K. N. Campbell, *et al.*, *J. Org. Chem.*, **11**, 404 (1946).

(6) (a) G. N. Walker and B. N. Weaver, *ibid.*, **25**, 184 (1960); (b) M. S. Brown and H. Rapoport, *ibid.*, **28**, 3261 (1963).

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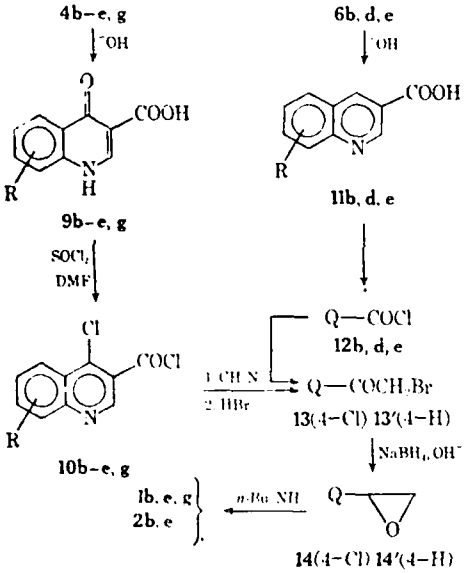
Subsequent S dehydrogenation of **7b** gave the desired quinoline **6b** (92%).

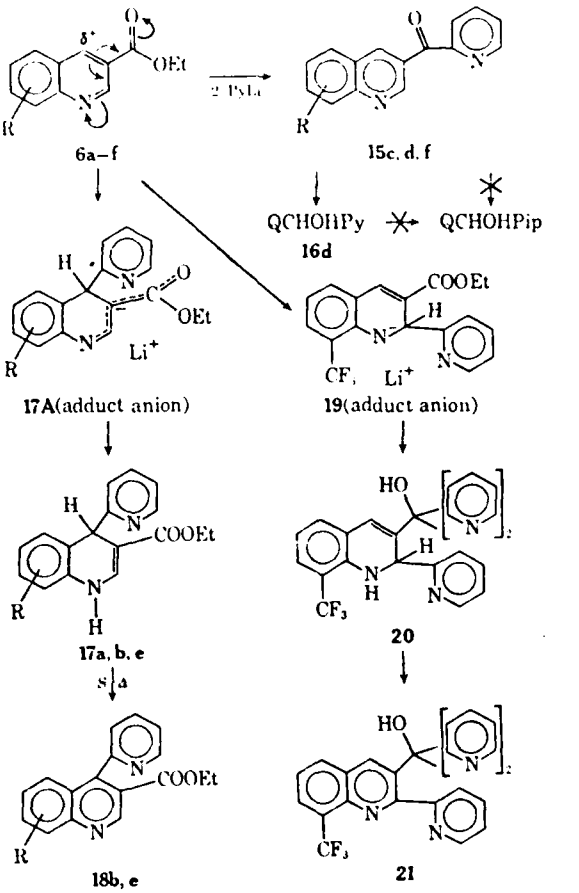
Interestingly, $NaBH_4$ in 2-methoxyethanol did not dehalogenate 6,8-dimethyl-4-chloro-3-carbethoxyquinoline but instead brought about reduction of the 3-carbethoxy group to the methanol **8c** (53%).

α-Di-*n*-butylaminomethyl-3-quinolinemethanols.—Seven of these, **1b-e, g**, and **2b, e**, were prepared by adaptations of the standard scheme.[7] The 3-carbethoxy-4-quinolones and quinolines **4b-e, g** and **6b, d, e** were converted into the acids **9b-e, g** and **11b, d, e** and then by $SOCl_2$ into the acid chlorides **10b-e, g** and **12b, d, e**. DMF was required as catalyst in the latter reaction with the quinolones. Diazomethylations of the acid chlorides followed by hydrobromination without isolation of the diazoketones gave the bromo ketones **13** and **13′**. These were converted into the epoxides **14** and **14′** by $NaBH_4$ reduction and dehydrohalogenation of the resulting bromohydrins by accompanying or subsequently added base. Condensation of the epoxides with n-Bu_2NH gave the target amino alcohols **1b-e, g** and **2b, e**.



α-(2-Piperidyl)-3-quinolinemethanols (3).—The Boykin procedure for the preparation of α-(2-pyridyl)-3-quinolyl ketones from 3-quinolinecarboxylic acids, by addition of 2-pyridyllithium followed by selective catalytic reduction of the pyridyl ring,[8] was not generally successful. Two of the acids without a substitutent in the 4 position, **11d** and **11e**, gave only low yields of the desired 2-pyridyl ketones **15d** and **e**.

The addition of 2-pyridyllithium to 3-carboxylic esters was therefore investigated with interesting results of limited usefulness. To a significant extent addition occurred at the carbethoxy group of the 6,8-dimethyl, 8-phenyl, and 6-methoxy esters **6c, d, f**, giving 2-pyridyl ketones **15c, d, f**, (15, 66, and 66%, respectively). On the other hand, the reactions with the parent ester and the 6,8-dichloro and 8-trifluoromethyl analogs, **6a, b, e**, gave the 4-(2-pyridyl)-1,4-dihydro-3-carbethoxyquinolines **17a, b, e** in yields of 0.7, 18, and 20%, respectively. The structures **17** were assigned on the basis of elemental analyses, ir and nmr spectra, and S dehydrogenation of two of them (**17b, e**) to the 4-pyridyl-3-carbethoxyquinolines **18b, e**. The nmr spectra of the latter, **18b, e**, showed characteristic quinoline H-2



protons as sharp singlets at δ 9.58 and 9.46, respectively, which were assignable as such on the basis of the known chemical shifts of δ 9.36 ± 0.02 for the H-2 protons of 4-phenyl-3-carbethoxyquinolines[9] and the distinctively upfield chemical shifts for the H-4 protons of 2-substituted quinolines.[10] Only in the reaction of **6e** was a second product isolated (11%), which appears to be the result of addition of pyridyllithium to the quinoline nucleus, and to which the structure **20**, α-bis(2-pyridyl)-2-(2-pyridyl)-1,2-dihydro-8-trifluoromethyl-3-quinolinemethanol, is tentatively assigned on the basis of elemental analysis, ir, nmr, and mass spectra, and S dehydrogenation to **21** where the nmr spectrum revealed a quinoline H-4 proton at δ 7.59 (see Experimental Section for comparison with nmr of **3c**) and no H-2 proton. In the above and presumably reversible Michael type addition of pyridyllithium to the crossconjugated system of **6** at the highly δ+ C-4, the expected or necessary adduct anion **17A** would be considerably stablized by resonance involving the ester CO and would resist further attack at the ester function. On the other hand ad-

(7) R. E. Lutz *et al.*, *J. Amer. Chem. Soc.*, **68**, 1814 (1946).

(8) (a) D. W. Boykin, Jr., A. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 129 (1967); (b) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, **11**, 273 (1968).

(9) N. D. Heindel, P. D. Kennewell, and C. J. Olanmacht, *J. Org. Chem.*, **34**, 1168 (1969).

(10) Japan Electron Optics Laboratory Co. Ltd., "JOEL High Resolution NMR Spectra," Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1967.

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dition at C-2 would yield intermediate anion **19** in which the ester function is conjugatively free for further reaction. Literature analogies for these reactions are seen in the addition of $PhCH_2MgBr$[11] and BuLi[12] to C-2 and C-4 of quinoline itself. The often low material balance in the PhLi additions is evident from Table I where

Table I

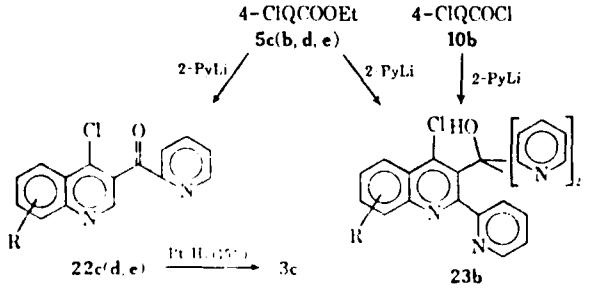
Chemical Shifts of H-2 and H-4 of Substituted 3-Carbethoxyquinolines 6

	R	Products (%)	H-2 δ	H-4 δ
6c	6,8-Me_2	**15c** (15)	9.50	8.42
f	6-OCH_3	**15f** (66)	9.38	8.73
b	6,8-Cl_2	**16b** (18)	9.51	8.74
e	8-CF_4	**16e** (20), **20** (11)	9.61	8.89
a	H	**16a** (0.8)	9.55	8.90
d	8-Ph	**15d** (66)	9.55	8.90

yields of products are compared with the H-2 and H-4 nmr chemical shifts which are a measure of substituent electronic effects on the two possible sites of initial nuclear attack. The seemingly anomolous behavior of the 8-Ph analog **6d** in respect to prediction based solely on its H-4 nmr chemical shift might be explained in terms of steric hindrance at the quinoline N toward coordination with 2-pyridyllithium.[13]

Unfortunately attempts to hydrogenate selectively the 2-pyridyl nucleus of either pyridyl ketones **15c**, **d**, **f** or α-(2-pyridyl)-8-phenyl-3-quinolinemethanol (obtained through $NaBH_4$ reduction of **15d**) yielded dark mixtures which were shown by tlc to be multicomponent. These results are in contrast to the usually successful reductions of the pyridyl rings of the 2-aryl types[3] where the 2 substitutent appears to permit these selective reductions, probably by sterically decreasing the facility of reduction of the N-containing ring of the quinoline nucleus.

The successful and fortuitious synthesis of one example of the desired α-(2-piperidyl)-6,8-dimethyl-3-quinolinemethanol (**3c**), stemmed from the work described below which was designed to obtain target analogs carrying Cl or some other heteroelemental group at position 4. This synthesis proceeded through the quinolone ester **4c** and the 4-chloro-(2-pyridyl) ketone **22c**. This ketone **22c** was unique in undergoing selective hydrogenation of the pyridyl nucleus with simultaneous reductive 4-dechlorination. This uniqueness possibly may be due to a combination of electronic stabilization by the electron-repelling Me groups and a steric effect of the 8-Me not unlike that of a 2-aryl group.

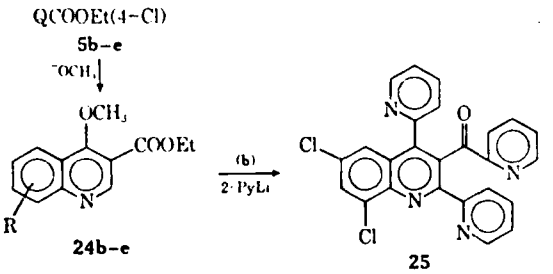


(11) E. Bergmann and W. Rosenthal, *J. Prakt. Chem.*, **135**, 267 (1932).
(12) K. Ziegler and H. Zeiser, *Justus Liebigs Ann. Chem.*, **485**, 174 (1931).
(13) (a) A. Kaufmann, P. Dandliker and H. Burkhardt, *Ber.*, **46**, 2929 (1913); (b) J. P. Wommack, T. G. Barbee, Jr., D. J. Thulness, M. A. McDonald and D. L. Pearson, *J. Heterocycl. Chem.*, **6**, 245 (1969).

The target amino alcohol **3c** was shown actually to be a mixture of difficultly separable diastereomers. This fact had not been revealed by tlc and became evident from the nmr spectrum of analytical samples which showed a pair of carbinol α-proton doublets of δ 4.56 (J = 8 Hz) and 4.85 (J = 5 Hz) in an integration ratio of 59:41 with total integration for one H. Work on this problem has not been undertaken because of the lack of significant antimalarial activity of the mixture and low priority in the malaria program.

The 4-chloro-3-carbethoxyquinolines **5c**, **d**, and **e** reacted with 2-pyridyllithium giving the desired 4-chloro-3-quinolyl 2-pyridyl ketones **22c**, **d**, and **e** in 63, 27, and 63% yields, respectively. The 6,8-dichloro analog **5b**, however, gave the 2-pyridyl-α-di-(2-pyridyl)carbinol **23b** (43%; shown by ir (λ 1700 cm^{-1}) to contain a small amount of an unisolated pyridyl ketone). The corresponding acid chloride **10b** gave only the carbinol **23b** in 34% yield.

Approaches to the Synthesis of 4-Methoxy- and 4-Diethylamino-3-quinoline-α-aminomethanols.—4-Methoxy-3-quinolinecarboxylate esters **24b–e** were easily prepared by the action of NaOMe on the 4-chloro esters **5b–e**. A representative of these, **24b**, reacted with 2-pyridyllithium but gave a tripyridyl derivative, 2,4-di-(2-pyridyl)-3-quinolyl 2-pyridyl ketone (**25**, 44%) which evidently was contaminated with a small amount of unidentified material of molecular weight 440 (mass spectrum). The structure of **25** was established by elemental analysis and by ir, mass, and nmr spectra. It is of interest to compare the above reaction with that of $PhCH_2MgBr$ at the 4 position of 2-methoxyquinoline (which did not at the same time displace the 2-MeO group),[14] and to contrast it to the displacement of the EtO group of 2-ethoxyquinoline by BuLi.[15]



Displacement of the 4-Cl of the 8-Ph ester **5d** by NET_2 gave the 4-diethylamino ester **26** which then upon reaction with 2 equiv of 2-pyridyllithium gave the dipyridyl carbinol **27**.

8-Trifluoromethyl-4-chloro-3-quinolyl 2-pyridyl ketone (**22e**) reacted with Et_2NH and with NaOMe to give the corresponding 4-diethylamino and 4-methoxy derivatives **28** and **29**. However, the desired α-piperidylmethanols were not obtained from these by catalytic reduction. One attempt to prepare a 4-*p*-chloroanilino derivative from the pyridyl ketone **22e** by reaction with *p*-chloroaniline and acidic work-up, involved hydrolysis of the 4-Cl and gave the 4-quinolone ketoanil **30** the structure of which is supported by analysis and nmr and ir spectra.

(14) R. C. Fuson, H. L. Johnson, and E. Greishaber, *J. Org. Chem.*, **16**, 1529 (1951).
(15) H. Gilman and J. A. Beel, *J. Amer. Chem. Soc.*, **73**, 774, 32 (1951).

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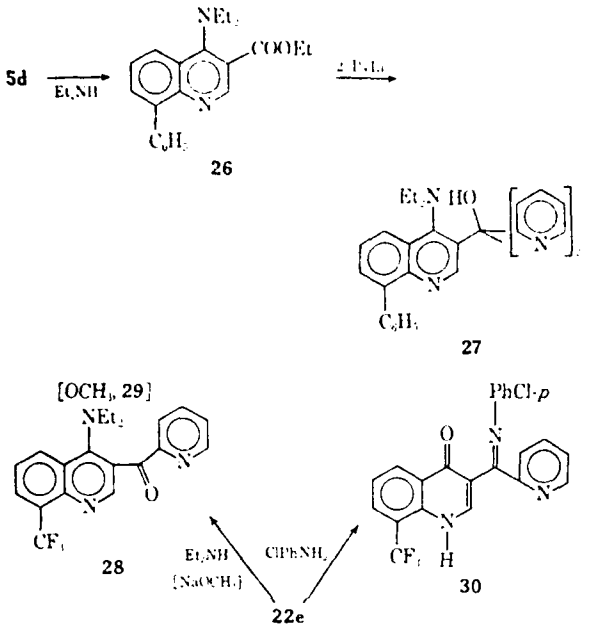
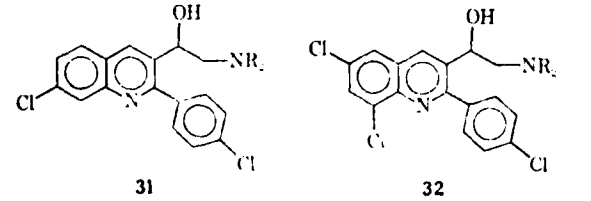


Because of unpromising pharmacological tests on the compounds **1**, **2**, and **3**, work on this series and on the several interesting unanswered chemical questions raised, has been suspended.

Biological Activity.—Antimalarial tests on compounds **1–3** were carried out on mice infected with *Plasmodium berghei* according to the method of Rane, *et al.*[16] Defining a drug as active when the mean survival time (MST) of the treated group is more than double that of controls (7.0 ± 0.5 days), and "curative" upon survival up to 60 days, **1** – **3** exhibited no antimalarial activity at the highest recorded dose level. The increases in survival times at 640 mg/kg in fractions of a day were: **1b**, 0.3; **1c**, 0.1 (at 320 mg/kg); **1d**, 0.4; **1e**, 9.4; **1g**, 0.5; **2b**, 0.5; **2e**, 0.3; and **3c**, 1.0.

In contrast to the above, six α-dialkylaminomethyl-2-*p*-chlorophenyl-3-quinolinemethanols (**31–32**) synthesized by Donovan and Smith [1d] possessed low antimalarial activities. The most active of these was **32b** which at 640 mg/kg increased the mean survival time 9.4 days.[16] This compound was phototoxic as determined by the method of Rothe and Jacobus; the minimum effective phototoxic dose was below 200 mg/kg in mice administered ip.[17] As a point of interest in this series, the 3-amino alcohol group must sterically interfere with the coplanarity and conjugation of the 2-aryl group with the quinoline nucleus, a conjugation with which the high phototoxicities in the 2-aryl-4-quinoline amino alcohols might possibly be associated.



(16) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). Test data were supplied by the Walter Reed Army Institute of Research, Washington, D. C.

(17) W. E. Rothe and D. P. Jacobus, *ibid.*, **11**, 366 (1968).

Experimental Section[18]

3-Carbethoxy- and 3-carboxy-4(1*H*)-quinolones (4 and 9) were prepared according to published procedures for the parent,[2c] 8-Ph,[3b] 6-MeO,[1c] and 7-Cl[1c] compounds. Ph_2O was employed as cyclization solvent in all preparations of **4**.

Quinolinecarbonyl Chlorides (10, 12). A. 4,6,8-Trichloro-3-quinolinecarbonyl Chloride (10b).—DMF (2 ml) was added to a stirred refluxing slurry of 10 g (0.035 mole) of **5b** and 50 ml of $SOCl_2$; refluxing was continued for 4 hr. Excess $SOCl_2$ was distilled at atm pressure and the last traces removed by codistillation with dry C_6H_6. Crystallization of the residue from pet ether (60–110°) gave 9.85 g (86%) of the yellow acid chloride **10b**, mp 145–148°.

B.—**12b** and **e** were prepared as above but without DMF catalyst.

α-Bromomethyl-3-quinolyl ketones (13, 13′) were prepared[7] through but without isolation of the intermediate diazomethyl ketones.

3-Quinolylethylene Oxides (14, 14′). A. 4,6,8-Trichloro-3-quinolylethylene Oxide (14b).—To a stirred slurry of 6.9 g (0.02 mole) of bromoethyl 4,6,8-trichloroquinolyl ketone (**13b**) in 50 ml of MeOH was added dropwise, over 10 min, a soln of 1.0 g (0.026 mole) of $NaBH_4$, 3 ml of *N* NaOH, and 10 ml of H_2O. The solid dissolved almost immediately and after 20 min a ppt formed. After an additional 1 hr of stirring the pale yellow product was collected and oven-dried: 4.4 g (82%); mp 131–133°.

B.—A modification of the above procedure was necessary for **14′b** and **e**.

6,8-Dichloro-3-quinolylethylene Oxide (14′b).—A refluxing slurry of 8.74 g (0.0274 mole) of the bromomethyl ketone **13′b** in 50 ml of MeOH was removed from the heat source and stirred while a soln of 2.0 g (0.053 mole) of $NaBH_4$ in 10 ml of H_2O was added dropwise over 10 min. Addition of 5 ml of 2 *N* NaOH to the stirred, clear yellow soln caused pptn of **14′b**: 4.84 g (74%); pale yellow; mp 112–115°.

α-Di-*n*-butylaminomethyl-3-quinolinemethanols (1, 2). α-Di-*n*-butylaminomethyl-4,6,8-trichloro-3-quinolinemethanol (1b).—A stirred soln of 5.3 g (0.019 mole) of **14b** and 35 ml of *n*-Bu_2NH was heated at 135° for 18 hr. After excess reagent was removed by vac distillation the orange residue was dissolved in dry Et_2O, and **1** was fractionally pptd by Et_2O–HCl (the last fractions tended to gum; total crude yield; 6.28 g (74%); recrystd from EtOH–Et_2O, 4.20 g (49%); mp 178–180° dec.

3-Carbethoxy-4-chloroquinolines (5) were prepared by the reaction of the 3-carbethoxyquinolones **4a–g** with $POCl_3$ (3 moles, 3 hr, reflux); **5a** and **5f**[19] had previously been prepared employing a $POCl_3$–PCl_5 mixture.

3-Carbethoxy-8-trifluoromethyl-1,4-dihydroquinoline (7e).—A mixture of 4.0 g (0.013 mole) of **5e**, 0.84 g (0.015 mole) of KOH, 0.4 g of 10% Pd-C, and 25 ml of abs EtOH, was hydrogenated at 55° for 2.5 hr at 3.52 kg/cm². Filtration through Celite, concentration, and filtering gave **7e**: 2.19 g (61%); mp 158–159°; nmr ($CDCl_4$) δ 7.17 (m, 4), 6.50 (m, 1), 4.25 (m, 2), 3.79 (s, 2), 1.36 (t, 3).

3-Carbethoxy-6,8-dichloro-1,4-dihydroquinoline (7b).—To a stirred, ice-cooled soln of 6.0 g (0.16 mole) of $NaBH_4$ in 125 ml of 2-methoxyethanol was added portionwise 19.1 g (0.063 mole) of **5b**. The first addition caused temp rise to 60° and liberation of gas. The remainder of **5b** was then added over 1 hr. The slurry was stirred for 3 hr and the resulting ppt (**5b** and **7b**) was air-dried: 12.17 g (orange); mp 105–180°. Retreatment of this as above with 4 g of $NaBH_4$ in 125 ml of 2-methoxyethanol for 3 hr yielded 6.61 g (39%) of **7b** (orange): mp 187.5–189.5°; anal. sample (EtOH), mp 196° dec; nmr (DMSO-d_6) δ 8.61 (m, 1), 7.19 (m, 3), 4.11 (q, 2), 3.67 (s, 2), 1.22 (t, 3). The mother liquors poured into H_2O gave 6.88 g (oven-dried), mp 130–160°. Extraction with refluxing pet ether (bp 60–110°) removed unreacted **5b**: recrystd from EtOH, 2.1 g of **8b** (13%); mp 193–198°.

3-Carbethoxyquinolines (6). Catalytic Dehalogenation. 3-Carbethoxy-8-phenylquinoline (6d).—The following improved

(18) *Instruments*: (a) Melting points were obtained on a Thomas-Hoover apparatus, uncorrected; (b) anal. were correct ±0.4%; Galbraith Lab. Inc., and Swartzkopf Microanalytical Lab; (c) sublimation of analytical samples was at 10–50° below the mp; (d) satisfactory spectra were obtained, for structural determination where required, and randomly in other cases, (e) ir, Perkin-Elmer 337; (f) nmr, Hitachi P-E R 20; (g) mass spectrograph, Hitachi P-E, RMU 6E.

(19) W. O. Kermack and N. Storey, *J. Chem. Soc.*, 1389 (1951).

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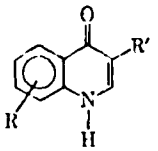
TABLE II

3-FUNCTIONALIZED-4-QUINOLONES

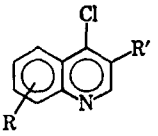


Compd	R	R′	Mp, °C[a]	% yield	Composition[e]
4b	6, 8-Cl_2	COOEt	305–308 dec[b]	74	$C_{12}H_9Cl_2NO_3$
9b	6, 8-Cl_2	COOH	300 dec[b]	100	$C_{10}H_5Cl_2NO_3$
4c	6, 8-Me_2	COOEt	273–276 dec[c]	68	$C_{14}H_{15}NO_3$
9c	6, 8-Me_2	COOH	298–300 dec[b]	100	$C_{12}H_{10}NO_3$
4e	8-CF_3	COOEt	209–213[c]	83	$C_{13}H_{10}F_3NO_3$
9e	8-CF_3	COOH	235 dec[d]	83	$C_{11}H_6F_3NO_3$
30	8-CF_3	C(2-Py)=NPhCl	199–200.5[c]	92	$C_{22}H_{13}ClF_3N_3O$[f]

[a] Dec, mp decomp. Recryst from: [b] DMF; [c] EtOH. [d] Analytically pure from reaction mixture. [e] Analyzed within ±0.4% for C, H; [f] for C, H, Cl, N.

TABLE III

3-FUNCTIONALIZED-4-CHLOROQUINOLINES



Compd	R	R′	Mp, °C	% yield	Composition[l]
10b	6, 8-Cl_2	COCl	145–147	90[a,b]	$C_{10}H_3Cl_4NO$
10c	6, 8-Me_2	COCl	103–105	38[a,b]	$C_{12}H_9Cl_2NO$
10d	8-Ph	COCl	125–126.5	90[a,b]	$C_{16}H_9Cl_2NO$[m]
10e	8-CF_3	COCl	94–95.5	70[a,b]	$C_{11}H_4Cl_2F_3NO$[m]
10g	7-Cl	COCl	137–139	38[a,b]	$C_{10}H_4Cl_2NO$
13b	6, 8-Cl_2	$COCH_2Br$	136–137.5	87[c]	$C_{11}H_5BrCl_3NO$
13c	6, 8-Me_2	$COCH_2Br$	76.5–78	58[a]	$C_{13}H_{11}BrClNO$
13d	8-Ph	$COCH_2Br$	132–133 dec	98[d]	$C_{17}H_{11}BrClNO$[m]
13e	8-CF_3	$COCH_2Br$	98–99	79[c]	(crude)
13g	7-Cl	$COCH_2Br$	104–106	83[a]	$C_{11}H_6BrCl_2NO$
14b	6, 8-Cl_2		132.5–134	82[a,b]	$C_{11}H_6Cl_2NO$
14c	6, 8-Me_2		95–96	91[a]	$C_{12}H_{12}ClNO$[j]
14d	8-Ph		140–141	83[f,b]	$C_{17}H_{12}ClNO$[j]
14e	8-CF_3		82–83	52[a]	$C_{12}H_7ClF_3NO$[k,m]
14g	7-Cl		153.5–155	83[c]	$C_{11}H_7Cl_2NO$
1b	6, 8-Cl_2	$CHOHCH_2NBu_2$	181–182 dec	74[g]	$C_{19}H_{27}Cl_3N_2O\cdot HCl$
1c	6, 8-Me_2	$CHOHCH_2NBu_2$	121–123 dec	66[g]	$C_{21}H_{31}ClN_2O\cdot HCl$
1d	8-Ph	$CHOHCH_2NBu_2$	174 dec	90[g]	$C_{25}H_{31}ClN_2O\cdot HCl$
1e	8-CF_3	$CHOHCH_2NBu_2$	172 dec	56[g]	$C_{20}H_{26}ClF_3N_2O\cdot HCl$
1g	7-Cl	$CHOHCH_2NBu_2$	168–170 dec	75[g]	$C_{19}H_{27}Cl_3N_2O\cdot HCl$
5b	6, 8-Cl_2	COOEt	109–110	87[f]	$C_{12}H_9Cl_2NO_2$[m]
5c	6, 8-Me_2	COOEt	76–77.5	97[f,b]	$C_{14}H_{14}ClNO_2$[m]
5d	8-Ph	COOEt	131–132.5	88[f]	$C_{18}H_{14}ClNO_2$[m]
5e	8-CF_3	COOEt	56–57	64[h]	$C_{13}H_9ClF_3NO_2$[m]
22c	6, 8-Me_2	COPy	148 dec	63[c]	$C_{17}H_{13}ClNO_2$
22d	8-Ph	COPy	102–103	27[c]	$C_{21}H_{13}ClN_2O$
22e	8-CF_3	COPy	155	63[c]	$C_{16}H_8ClF_3N_2O$
8b	6, 8-Cl_2	CH_2OH	196–198	13[c]	$C_{10}H_6Cl_2NO$[m]
8c	6, 8-Me_2	CH_2OH	166–169	53[c]	$C_{12}H_{12}ClNO$[m]

Recrystd from: [a] Pet ether (bp 60–110°); [b] sublimed; [c] EtOH; [d] crude, EtOH washed; [e] MeOH; [f] hexane; [g] EtOH–Et_2O. [h] pet ether (bp 50–60°). [i] C, calcd 66.81, found 65.99. [j] C: calcd 72.47, found 71.00. [k] C: calcd 52.67, found 52.13. [l] *Anal.*[m] for C,H,N; [m] for C,H only.

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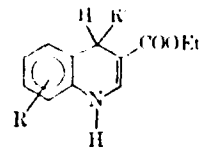
TABLE IV

1,4-DIHYDRO-3-QUINOLINE CARBOETHOXYLATES

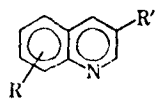


Compd	R	R'	Mp, °C	% yield	Composition[f]
7b	6, 8-Cl_2	H	196 dec[a]	39	$C_{13}H_{11}Cl_2NO_2$
7e	8-CF_3	H	158–159[b]	61	$C_{13}H_{12}F_3NO_2$
17a	H	2-Py	199–201[a,c]	0.7	$C_{17}H_{16}N_2O_2$[g]
17b	6, 8-Cl_2	2-Py	221–222 dec[d]	18	$C_{17}H_{14}Cl_2N_2O_2$
17e[e]	8-CF_3	2-Py	175–176[a]	20	$C_{18}H_{15}F_3N_2O_2$[h]

Recrystn solvent: [a] EtOH; [b] hexane; [c] sublimed; [d] 2-methoxyethanol. [e] Nmr ($CDCl_3$) δ 8.56 (d, 1), 7.32 (m, 8), 5.40 (s, 1), 4.10 (m, 2), 1.14 (t, 3). [f] *Anal.*[19b] C,H,N; [g] C: calcd 72.83; found 73.47; [h] for C,H only.

TABLE V

3-FUNCTIONALIZED QUINOLINES



Compd	R	R'	Mp, °C	% yield	Composition[m]
6b	6, 8-Cl_2	COOEt	131–133	96[a]	$C_{12}H_9Cl_2NO_2$
6c	6, 8-Me_2	COOEt	80.5–81	51[b]	$C_{14}H_{15}NO_2$[n]
6d	8-Ph	COOEt	106–107	54[c]	$C_{18}H_{15}NO_2$[n]
6e	8-CF_3	COOEt	88–89.5	73[c]	$C_{13}H_{10}F_3NO_2$[n]
6f	6-OMe	COOEt	85–87	66[b]	$C_{13}H_{13}NO_3$[n]
11b	6, 8-Cl_2	COOH	300–301 dec	94[d]	$C_{10}H_5Cl_2NO_2$[n]
11d	8-Ph	COOH	205–206	70[e]	$C_{16}H_{11}NO_2$[n]
11e	8-CF_3	COOH	208–209	78[c]	$C_{11}H_6F_3NO_2$[n]
12b	6, 8-Cl_2	COCl	170–172	92[a,f]	$C_{10}H_4Cl_3NO$
12e	8-CF_3	COCl	94–95	56[f,g]	$C_{11}H_5ClF_3NO$[n]
13′b	6, 8-Cl_2	$COCH_2Br$	197–199 dec	81[h]	$C_{11}H_6BrCl_2NO$
13′e	8-CF_3	$COCH_2Br$	142–143	66[c]	$C_{12}H_7BrF_3NO$
14′b	6, 8-Cl_2		118.5–120	74[g]	$C_{11}H_7Cl_2NO$
14′e	8-CF_3		65–67	72[f,g]	$C_{12}H_8F_3NO$
2b	6, 8-Cl_2	$CHOHCH_2NBu_2$	65–72 dec	38[i]	$C_{19}H_{26}Cl_2N_2O \cdot HCl$
2e	8-CF_3	$CHOHCH_2NBu_2$	90.5–92 dec	59[i]	$C_{20}H_{27}F_3N_2O \cdot HCl$
15c	6, 8-Me_2	COPy	97.5–98	27[a,f]	$C_{17}H_{14}N_2O$
15d	8-Ph	COPy	118–118.5	66[c,k,l]	$C_{21}H_{14}N_2O$[n]
15e	8-CF_3	COPy	99–99.5	58[c,l]	$C_{16}H_9F_3N_2O$[n]
15f	6-OMe	COPy	129–131.5	66[c]	$C_{16}H_{11}N_2O_2$
3	6, 8-Me_2	CHOHPip	143–148	15[f,k]	$C_{17}H_{22}N_2O$
16d	8-Ph	CHOHPy	137.5–138	64[c]	$C_{21}H_{16}N_2O$[n]

Recrystd from: [a] pet ether (60–100°), [b] (30–60°); [c] EtOH; [d] 2-methoxyethanol; [e] reaction product Et_2O washed; [f] sublimed; [g] hexane; [h] MeCN; [i] hygroscopic, not crystd; [j] EtOH–Et_2O; [k] prepared by the action of 2-PyLi on the 3-carboxylate ester; [l] by 2-PyLi on the 3-carboxylic acid (**15d**, 32%). [m] *Anal.*[19b] for C,H,N; [n] for C,H only.

method of Kaslow and Clark was used to prepare **6a**.[4] A suspension of 4.0 g (0.013 mole) of **5d** and 0.6 g of 10% Pd–C in 25 ml of glacial AcOH at 50° was hydrogenated (1 hr, 3.16 kg/cm²). Filtration through Celite, pouring into H_2O with stirring, collection of the ppt by filtration, and crystn from hexane gave 1.92 g (54%), mp 106–107°.

Sulfur Dehydrogenation of a 1,4-Dihydroquinoline. 3-Carbethoxy-6,8-dichloroquinoline (6b). An intimate mixture of 11.9 g (0.044 mole) of **7b** and 3.13 g (0.097 mole) of S in a Wood's metal bath at 190°, was heated at 230° for 15 min (cessation H_2S evolved vigorously). Cooling, extraction with 300 ml of refluxing pet ether (60–110°), filtering, concentrating to 125 ml, cooling, and recrystn of the yellow ppt from 250 ml of pet ether gave 11.45 g (96%), mp 132–134°.

4-Methoxy-3-carbethoxyquinolines (21). 4-Methoxy-6,8-dichloro-3-carbethoxyquinoline (21b). A soln of 17.5 g (0.058 mole) of **5b** in 400 ml of MeOH was added to a soln of 0.17 mole of NaOMe in 150 ml of MeOH. After 1-hr reflux the mixture was poured into 2 l. of H_2O giving 13.9 g (80%), oven-dried, mp 141–142.5°.

4-Diethylamino-8-phenyl-3-carbethoxyquinoline (26). A soln of 6.2 g (0.02 mole) of **5d** and 4.4 g (0.06 mole) of Et_2NH in 100 ml of EtOH was refluxed for 2 hr. Cooling in ice returned 2.25 g (37%) of **5d**. Extraction of the residue from evapn of the filtrate with hexane, filtration to remove Et_2NH·HCl, and evapn to dryness gave 3.1 g of **26**.

***2-Pyridyllithium* Reactions. A. With Carboxylic Acids 11 d,e. 2-Pyridyl 8-Phenyl-3-quinolyl Ketone (15d).**—To a stirred soln of 2-pyridyllithium[20a,20b] (from 11 g of 2-bromopyridine in 150 ml of anhyd Et_2O at −70° under N_2) was added rapidly

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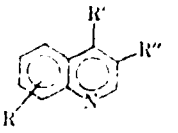
TABLE VI

3-FUNCTIONALIZED-4-SUBSTITUTED QUINOLINES

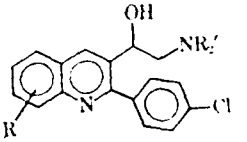


Compd[a]	R	R′	R″	Mp, °C	% yield[b]	Composition[b]
24b	6, 8-Cl_2	OMe	COOEt	141.5–143	80[c,d]	$C_{21}H_{21}Cl_2NO_3$[f]
24c	6, 8-Me_2	OMe	COOEt	83.5–85	56[d,e]	$C_{23}H_{27}NO_3$[f]
24d	8-Ph	OMe	COOEt	135.5–136	87[c]	$C_{27}H_{27}NO_3$[f]
24e	8-CF_3	OMe	COOEt	79.5–80	70[c]	$C_{24}H_{22}F_3NO_3$[f]
18b	6, 8-Cl_2	Py	COOEt	100–101.5	48[f]	$C_{17}H_{12}Cl_2N_2O_2$
18e	8-CF_3	Py	COOEt	64–66	15[f]	$C_{18}H_{13}F_3N_2O_2$
26	8-Ph	NEt_2	COOEt	72–74	72[c]	$C_{22}H_{24}N_2O_2$[f]
27[g]	8-Ph	NEt_2	C(OH)Py_2	200–201	14[f]	$C_{30}H_{28}N_4O$
28	8-CF_3	NEt_2	COPy	130.5–131	60[f]	$C_{20}H_{19}F_3N_2O$
29	8-CF_3	OMe	COPy	172.5–174	37[c,d]	$C_{17}H_{11}F_3N_2O_2$
23[h]	6, 8-Cl_2	Cl	C(OH)Py_2[h]	197–199	34[c,i]	$C_{25}H_{16}Cl_3N_3O$

[a] Py = 2-pyridyl. [b] Recryst from: [c] MeOH; [d] sublimed; [e] hexane; [f] EtOH. [g] Nmr ($CDCl_3$) δ 10.86 (s, 1), 8.87 (s, 1), 8.47 (d, 2), 7.51 (m, 14), 3.40 (m, 4), 1.05 (t, 6). [h] Also carries 2-(2-Py). [i] Prepared from acid chloride. [j] Prepared from ester, 47%. [k] *Anal.*[19b] for C,H,N; [l] for C,H only.

TABLE VII[a]

α-DIALKYLAMINOMETHYL-2-(*p*-CHLOROPHENYL)-3-QUINOLINEMETHANOLS[a]



Compd[a]	R	R′	Mp, °C	% yield	Composition[c]
31a	7-Cl	Et	113–115	72	$C_{21}H_{22}Cl_2N_2O$
31b	7-Cl	Bu	185–186.5	76	$C_{23}H_{26}Cl_2N_2O$·HCl
31c	7-Cl	Heptyl	171–172.5	62	$C_{31}H_{42}Cl_2N_2O$·HCl
32a	6, 8-Cl_2	Et	133–134	83	$C_{21}H_{21}Cl_3N_2O$
32b	6, 8-Cl_2	Bu	227.5–230	71	$C_{25}H_{29}Cl_3N_2O$·HCl
32c	6, 8-Cl_2	Heptyl	162–164.5[b]	73	$C_{31}H_{40}Cl_3N_2O$·HCl

[a] Synthetic route: 6-Cl-isatin, *p*-Cl-propiophenone → Q-3-CH_3, 4-COOH → Q-3-CH_3 → Q-3-COOH → Q-COCl → Q-$COCHN_2$ → Q-$COCH_2Br$ → Q-CHOHCH_2Br → Q-CH−CH_2 (O) → **31** and **32**. [b] Solidifying and again melting at 177–178°. [c] *Anal.*[19b] C,H,Cl,N.

2.48 g (0.01 mole) of **11d**. After 10 min 50 ml of anhyd THF (distd from CaH_2) was added, and stirring at −70° was continued for 3 hr. The mixture was allowed to warm to 40° and 100 ml of H_2O was added rapidly. After filtration to remove the insol pyridyl ketone (other such ketones are sol in Et_2O) the Et_2O layer was washed twice with H_2O and evapd under reduced pressure, giving additional **15d**: recrystd from abs EtOH, 1.0 g (32%); mp 118–118.5°.

B. With Esters.—A THF soln of the ester was added to a two- to threefold excess of 2-pyridyllithium. Usually the product was isolated by evaporation of the Et_2O and crystallization of the residue from EtOH. In the prepn of **22d** and **27**, unreacted starting material crystallized first from EtOH. In a slightly different work-up, before further purification was carried out, unreacted starting ester was extracted from crude **15c** and **17b** with petroleum pentane (30–60°) and hexane, respectively.

8-Trifluoromethyl-4-(2 pyridyl)-1,4-dihydroquinoline (17e).—**Reaction of ester 6e** (3.4 g, 0.013 mole), work-up as above, and fractional crystallization from EtOH yielded two products: **20**, 0.50 g (11%), mp 238.5–240°; ir (KBr disk), 3300 cm^{-1} (C-OH; no CO band); [*Anal.* ($C_{24}H_{15}F_3NO$) H, N; C: calcd 67.82; found 66.87; mol. wt calcd and found 393 (mass spectroscopy).] and **17e**, 0.88 g (20%), mp 175–176°; nmr ($CDCl_3$), δ 8.56 (d, 1), 7.32 (*m*, 8), 5.40 (s, 1), 4.10 (m, 2), 1.14 (t, 3). Compound **20** was dehydrogenated by S to yield a small amount of **21**, identified on the basis of the nmr spectrum which exhibited a sharp singlet at δ 7.59 (H-4) and an aromatic multiplet (δ 6.58–8.58).

2-Pyridyl 2,4-Di(2-pyridyl)-6,8-dichloro-3-quinolyl Ketone (25). The 2-pyridyllithium reaction mixture was stirred for only 1 hr after addition of the ester **24b**. Crystallization from EtOH gave 44% of starting ester **24b**. Evaporation of the filtrate and column chromatography of the residue on Florisil (MeOH in C_6H_6 gradient elution) gave a red amorphous solid which contained trapped solvent (by nmr). Crystallization from acetone (upon slow evaporation) gave 25% of **25** (yellow, true yield 45%); mp 234–238°; recrystd from MeCN, mp 239–241°, mol wt, calcd and found 457 (mass spectroscopy). *Anal.* ($C_{25}H_{14}Cl_2N_4O$: H,[19b] N,[19b] C, calcd, 65.66, found 66.28.

2-Pyridyl 4-Diethylamino-8-trifluoromethyl-3-quinolyl Ketone (28).—A soln of 1 g (2.96 mmoles) of **21e** and 0.890 g (11.8 mmoles) of Et_2NH in 15 ml of EtOH was refluxed for 1 hr. Ice-bath cooling gave 0.67 g (60%) of crude **28**.

2-Pyridyl 8-Trifluoromethyl-4(1*H*)-3-quinolonyl Ketone 4-Chlorophenylimine (30). A mixture of 2 g (5.95 mmoles) of **22d** and 2.3 g (18 mmoles) of 4-chloroaniline in 75 ml of EtOH was refluxed for 1 hr. Concentrated HCl (1 ml) was added and refluxing continued for another hour. The mixture was cooled and quenched in ice H_2O containing excess KOH. Crystallization of the ppt from EtOH gave 2.54 g (92%): nmr (DMSO-d_6) δ 9.56 (s, 1), 8.79 (s, 1), 8.64 (d, 2), 8.25 (d, 1), 7.71 (m, 4), 6.81 (m, 4).

α-(2-Piperidyl)-6,8-dimethyl-3-quinolinemethanol (Stereoisomer Mixture 3c).—A slurry of 9.0 g of **22c** (0.03 mole), 250 ml of abs EtOH, 6 ml of concd HCl, and 0.75 g of PtO_2 was hydrogenated at 3.15 kg cm^2. After absorption of $5H_2$, filtration through Celite, and concn to 30 ml, the soln was dild with H_2O and basified (NaOH). The Et_2O extract of the gummy ppt was washed with H_2O, dried ($MgSO_4$), and evapd. Treatment of the residual gum in 50 ml of Me_2CO with 75 ml of hexane and cooling gave 3.12 g (28%), mp 115–131°. Recrystallization from pet ether (60°–110°) and sublimation [150°(0.1 mm)] gave 1.23 g (15%), mp 143–148° (softens at 135°). An analytical sample was prepared by recrystn from MeCN: nmr ($CDCl_3$) δ 8.83 (d, 1, J = 2.5 Hz, H-2), 7.86 (q, 1, J = 2.5 Hz, nonequiv H-4 of diastereomers); 7.32 (s, 2), 4.85 (d, 0.41, J = 5 Hz), 4.56 (d, 0.59, J = 8 Hz), 4.21 (s, 2, NH_2OH), 2.75 (s, 3), 2.46 (s, 3), 2.7 (m, 3), 1.45 (m, 6).

Antimalarials. III. Benzothiazole Amino Alcohols[1a]

Journal of Medicinal Chemistry, 11, [illegible] (1968)

Alfred Burger[1b] and S. N. Saw[illegible]

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

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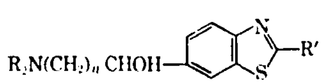
Amino alcohols carrying a $CHOH(CH_2)_n NR_2$ chain in position 6 of a benzothiazole nucleus, unsubstituted or substituted by phenyl or trifluoromethyl in the 2 position, have been synthesized by standard methods and tested for activity against *Plasmodium berghei* in mice. Several of the amino alcohols showed weak antimalarial activity but only at toxic doses.

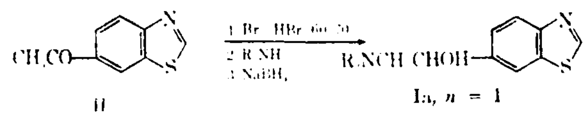
Bioisosteric substitution of benzothiazole for quinoline has been tried on three occasions,[2-4] each time for derivatives containing the dialkylaminoalkylamino chain characteristic of the prototypes, pamaquine and chloroquine. Only one group of authors[2] reported lack of antimalarial activity for their compounds, while the others[3,4] left biological behavior as unfinished business. In view of the renewed interest in amino alcohols incorporating some features of the quinine molecule[5] we investigated amino alcohols derived from benzothiazole as an extension of our studies of quinoline analogs.

All of the amino alcohols described in this paper carry the functional side chain in position 6 (I), that is, *para* to the ring nitrogen. This simulates a relationship to the 4-substituted quinoline amino alcohols as far as the benzothiazole system permits. Apart from the otherwise unsubstituted derivatives (Ia), 2-phenyl-substituted derivatives (Ib) were also prepared because 2-phenyl substitution in the quinoline series had proved advantageous to antimalarial potency,[6] perhaps due to inhibition of oxidative biotransformation. However, since the 2-phenyl-substituted quinolineamino alcohols cause photosensitization[7] and this may be associated with their increased conjugation,[8] 2-trifluoromethyl-substituted benzothiazoleamino alcohols (Ic) were prepared to avoid this effect; in the quinoline series, $2\text{-}CF_3$ substitution furnished amino alcohols with moderate antimalarial activity and less photosensitizing properties.[9]



Ia, R′ = H
b, R′ = C_6H_5
c, R′ = CF_3
n = 1-3; R_2N = dialkylamino, piperidino

Chemistry.—For the synthesis of amino alcohols of type Ia (n = 1) p-aminoacetophenone was thiocyanated[10] and then converted to 5-acetyl-2-aminobenzenethiol[11] and this was cyclized with formic acid to 6-benzothiazolyl methyl ketone (II). Bromination of II was followed by treatment of the resulting bromo ketone with secondary amines and reduction of the amino ketones.



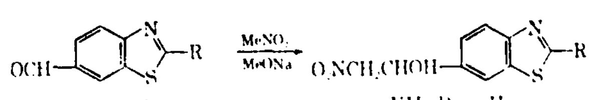
II   Ia, n = 1

The 2-phenyl (Ib, n = 1) and 2-trifluoromethyl (Ic, n = 1) analogs were obtained essentially by similar routes, benzoyl chloride[12] and trifluoroacetic anhydride, respectively, being used in dimethylaniline solution in the ring closure instead of formic acid. The bromination of the 2-substituted 6-benzothiazolyl methyl ketones in acetic acid always led to mixtures of mono- and dibromo ketones from which the monobromo ketone could be separated by repeated crystallization.

6-[3-Dimethylamino- (and piperidino-) 1-hydroxypropyl]benzothiazoles (Ia-c, n = 2) were prepared by reduction of the corresponding Mannich bases.

The synthesis of one example of a 6-(4-dialkylamino-1-hydroxybutyl)-2-phenylbenzothiazole [Ib, n = 3; R_2N = $N(CH_3)_2$] was accomplished by reducing ethyl 2-phenyl-6-benzothiazolecarboxylate (III, R = C_6H_5) to 2-phenyl-6-benzothiazolemethanol (IV), oxidizing IV to 2-phenyl-6-benzothiazolealdehyde (VI), and condensing this with γ-dimethylaminopropylmagnesium chloride (Scheme I).

The 2-unsubstituted aldehyde (V) was prepared by a similar sequence. Condensation of V and of VI with nitromethane yielded 1-(6-benzothiazolyl)-2-nitroethanol (VII) and its (2-phenyl-6-benzothiazolyl) derivative (VIII), respectively. Attempts to reduce these nitro alcohols to primary amino alcohols failed.



V, R = H
VI, R = C_6H_5

VII, R = H
VIII, R = C_6H_5

Biological Data. The twelve amino alcohols designated with Arabic numerals in Table I have been tested for activity against *Plasmodium berghei* in the mouse by the procedure of Rane, *et al.*[13] Deaths occurring on days 2-5 after infection were attributed to drug action; infected control animals did not die before day 6. These compounds were highly toxic at 160-640 mg/kg. They exhibited negligible antimalarial action at lower doses, were not curative at 10-640 mg/kg, and increased survival time from 0.3-2.9 days

(1)(a) This work was supported by the U. S. Army Medical Research and Development Command, Contract DA-49-193-MD-2955, Contribution No. 298. (b) To whom inquiries should be directed. (c) On leave of absence from Kurukshetra University, Kurukshetra (Haryana), India.

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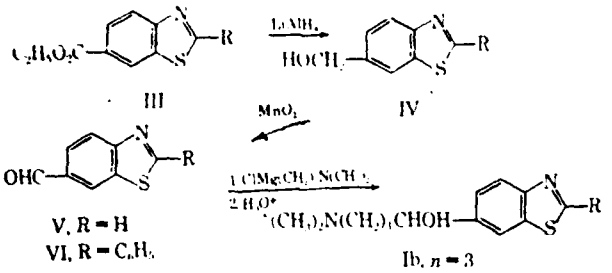
only. Substitution by phenyl or trifluoromethyl at position 2 did not affect antimalarial behavior.[14]

SCHEME I



Experimental Section

Melting points (taken in a heating bath) and boiling points are uncorrected. Ir spectra (KBr) were taken on a Perkin-Elmer Spectrocord and agreed with expected absorption bands. Where analyses in Table I are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Yields, physical data, and solvents are listed in Table I.

6-Acetylbenzothiazole (II).—A stirred mixture of 4-amino-3-thiocyanoacetophenone[10,11] (48 g, 0.25 mole), $Na_2S \cdot 9H_2O$ (72 g), and H_2O (150 ml) was heated under reflux for 45 min, cooled, and filtered from some undissolved material. The filtrate was neutralized carefully with AcOH. The semisolid was extracted into ether, washed (H_2O), and dried ($MgSO_4$), and the residue from the ether solution was refluxed with 90% formic acid (64 g) and a spatula-full of Zn dust for 3 hr. The cooled dark mixture was stirred into H_2O (400 ml), and the yellow solid which separated was filtered off, washed (H_2O), dried, and crystallized (C_6H_6–petroleum ether (bp 30–60°), then EtOH), yield 30.5 g.

6-Acetyl-2-phenylbenzothiazole.—4-Amino-3-mercaptoacetophenone was converted to its hydrochloride with dry HCl in ether. The salt (30.5 g, 0.15 mole) was dissolved in dimethylaniline (210 ml) and the solution was treated slowly, with stirring and cooling, with 30 g (0.21 mole) of benzoyl chloride. After heating under reflux for 1 hr, the mixture was cooled, poured into 1300 ml of 3.9% HCl, and stirred for 2 hr. The solid ketone was filtered off, washed (H_2O), dried, and recrystallized from C_6H_6 yielding 28 g of pale yellow shiny flakes.

In a similar manner, 6-(2-trifluoromethylbenzothiazolyl) methyl ketone was prepared, using 0.29 mole of $(F_3CCO)_2O$/0.2 mole of starting aminothiol ketone. For additional data see Table I.

6-Bromoacetylbenzothiazole.—A solution of Br_2 (16 g, 0.1 mole) in 48% HBr (100 ml) was added dropwise to a hot stirred solution of ketone II (17.7 g, 0.1 mole) in 200 ml of 48% HBr over a period of 1 hr, the mixture being maintained at 60–65°. After additional stirring for 2 hr at 60–65° the mixture was cooled to 0° and the crystalline salt which separated was filtered off. This salt was stirred well with H_2O, filtered, washed (H_2O), dried, and crystallized from C_6H_6 as pale brown crystals, yield 19 g.

6-Bromoacetyl-2-phenylbenzothiazole.—A solution of 6-acetyl-2-phenylbenzothiazole (7.6 g, 0.03 mole) in AcOH (100 ml) was refluxed until clear. A solution of Br_2 (4.8 g, 0.03 mole) in AcOH (30 ml) was then added dropwise over 1 hr and refluxing was continued for another hour. A light yellow solid separated from the cooled solution. It was filtered off, washed (H_2O), dried, and recrystallized three times from C_6H_6 to separate the product from dibromoacetyl material; yield 4.5 g.

6-Dialkylamino- (or piperidino-) acetylbenzothiazoles.—The respective 6-bromoacetylbenzothiazoles were treated with a secondary amine in dry benzene or ether as specified in the footnotes to Table I. The precipitated amine hydrobromide was filtered off, and the filtrate was washed (H_2O), dried, and concentrated at reduced pressure. Solid amino ketones were purified by crystallization. Liquid products were reduced without purification.

(14) These test data were supplied by the Walter Reed Army Institute of Research, Washington, D. C.

6-[2-Dialkylamino- (or piperidino-) 1-hydroxyethyl]benzothiazoles (I, n = 1).—The appropriate aminomethyl ketone (0.02 mole) was dissolved or suspended in MeOH (50 ml) and a solution of $NaBH_4$ (0.01–0.015 mole) in H_2O (5 ml) and 2 N NaOH (1 ml) was added gradually with stirring at about 15°. After stirring the mixture for 3–5 hr at 25° about half of the solvent was removed, and the mixture was diluted with H_2O and allowed to stand overnight. Solid amino alcohols were collected, washed (H_2O), and recrystallized. Liquid products were extracted (Et_2O), dried, and converted to common salts. If these failed to crystallize, 1,1′-methylenebis(2-hydroxy-3-naphthoate) salts were prepared for testing purposes. Picrates for characterization were usually prepared in ether.

Mannich Bases.—A solution of a 6-benzothiazolyl methyl ketone (0.05 mole), a secondary amine hydrochloride (0.055 mole), paraformaldehyde (0.08–0.12 mole), and 1–2 ml of ethereal HCl in 3-methylbutanol (50 ml) was refluxed. If the reaction required 12 hr, the paraformaldehyde was added in two to three portions. The β-amino ketone hydrochlorides either crystallized on cooling or could be precipitated with ether. The bases were liberated with aqueous Na_2CO_3, purified, and reconverted to hydrochlorides in dry ether.

6-[3-Dimethylamino- (or piperidino-) 1-hydroxypropyl]benzothiazoles (I, n = 2).—The Mannich bases were obtained from their hydrochloride salts in MeOH–2 N NaOH and reduced with $NaBH_4$ as described for the preparation of I (n = 1) above.

6-Benzothiazolecarboxylic Acid (III, R = H) and Ethyl Ester.—A stirred mixture of ethyl 4-amino-3-thiocyanobenzoate[10] (22.2 g, 0.1 mole), $Na_2S \cdot 9H_2O$ (29 g, 0.12 mole), and H_2O (60 ml) was refluxed for 45 min, cooled, and filtered from any undissolved material. The filtrate was neutralized with AcOH, and the precipitating semisolid aminothiol was extracted (Et_2O), washed (H_2O), and dried ($MgSO_4$). Ether was removed under reduced pressure, and the residual aminothiol was cyclized by refluxing with 25 g of 90% formic acid and a little Zn dust for 3 hr. The cooled reaction mixture was poured into cold water, the slowly solidifying material was filtered off and boiled with 5% $NaHCO_3$, and the solid was again filtered off after cooling. It was dissolved in ether, dried ($MgSO_4$), and distilled. The ester had bp 122–125° (0.2 mm), yield 11.5 g.

The $NaHCO_3$ solution was acidified to furnish 3 g of the free acid.

Ethyl 2-Phenyl-6-benzothiazolecarboxylate (III, R = C_6H_5).—A crude mixture (11.7 g) of ethyl 4-amino-3-mercaptobenzoate and 4-amino-3-mercaptobenzoic acid hydrochlorides was dissolved in 75 ml of dimethylaniline and treated gradually, with cooling and stirring, with 10 g of benzoyl chloride. After refluxing for 90 min the mixture was cooled and poured into 400 ml of 9% HCl. A solid precipitated, was filtered off, and worked up as above.

6-Benzothiazolemethanol (IV, R = H) and 2-phenyl-6-benzothiazolemethanol (IV, R = C_6H_5) were prepared by reduction of ethyl 6-benzothiazolecarboxylate and ethyl 2-phenyl-6-benzothiazolecarboxylate, respectively, with $LiAlH_4$ by the method of Zubarovskii and Khodot.[15] Oxidation of these alcohols (0.05 mole) with active MnO_2 (80 g) in dry $CHCl_3$ (1 l.) at 27° for 24 hr, filtration from MnO and removal of the solvent gave **6-benzothiazolecarboxaldehyde (V)** and **2-phenyl-6-benzothiazolecarboxaldehyde (VI)**, respectively.

6-(4-Dimethylamino-1-hydroxybutyl)-2-phenylbenzothiazole (Ib, n = 3; R = C_6H_5).—A solution of 1.5 g (0.012 mole) of γ-dimethylaminopropyl chloride in THF (2 ml) was added dropwise to a stirred mixture of Mg (0.3 g, 2 mg-atoms), dry THF (2 ml), and I_2 (one crystal) which had been activated with 0.1 ml of MeI. When the vigorous reaction had subsided the mixture was heated at 60° for 4 hr, another 0.2 g of γ-dimethylaminopropyl chloride was added, and heating was continued for 1 hr. A solution of aldehyde VI (1.2 g, 5 mmoles) in THF (15 ml) was then added dropwise at 20–30°, and the mixture was stirred and heated at 40–50° for 3 hr. It was decomposed with ice-cold saturated NH_4Cl and allowed to stand overnight. Ether and a little H_2O were added, the ether layer was separated, and the aqueous layer was extracted with ether. The combined ether extracts were dried ($MgSO_4$), the solvent was removed, and the residue was crystallized from petroleum ether, yielding 0.8 g of product.

(15) V. M. Zubarovskii and G. P. Khodot, *J. Gen. Chem. USSR*, **30** 1268 (1960).

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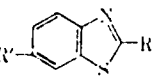
6-(1-Hydroxy-2-nitroethyl)benzothiazole (VII).—A solution of 6-benzothiazolecarboxaldehyde (V) (3.25 g, 0.02 mole) and $MeNO_2$ (1.25 g, 0.02 mole) in dry Et_2O (75 ml) was added to a mixture of 4 ml of 5 *N* NaOMe in MeOH and ether (10 ml) over a period of 10 min. After being stirred at 28° for 1 hr, the mixture was treated with AcOH (3 ml) in ether (20 ml) and stirred for another 15 min, and NaOAc was filtered off and washed with ether. The residue from the ether solution was a pale yellow solid. It was washed (H_2O) and dried and weighed 3.85 g.

TABLE I

DERIVATIVES OF BENZOTHIAZOLE[a]



No.	R	R′	% yield	Solvent of cryst.[b]	Mp, °C	Formula	Analyses
	H	$COCH_3$	69	PE–C_6H_6	94–95	C_9H_7NOS	C, H, N
	H	$COCH_2Br$	74	C_6H_6	133–135[c]	C_9H_6BrNOS	C, H, Br
1	H	$CHOHCH_2N(C_2H_5)_2 \cdot 2HBr$[d]	70	$MeNO_2$	110–112	$C_{13}H_{20}Br_2N_2OS$	C, H, N
		·Picrate		MeCN	178–180	$C_{19}H_{21}N_5O_8S$	C, H, N
	H	$CHOHCH_2N(C_4H_8)_2$[d]	69				
2		·1,1′-Methylenebis(2-hydroxy-3-naphthoate)[e]			128–130[f]	$C_{36}H_{42}N_2O_7S$	C, H, N
		·Picrate·HBr[g]		EtOH	153–154	$C_{23}H_{16}BrN_5O_9S$	C, H, N
3	H	$CHOHCH_2NC_5H_{10}$[h,i,j]	72	PE, EtOH	115–116	$C_{14}H_{18}N_2OS$	C, H, N
	H	$CO(CH_2)_2N(CH_3)_2 \cdot HCl$[j]	42	MeOH	210 dec	$C_{12}H_{15}ClN_2OS$	C, H, N
	H	$CO(CH_2)_2NC_5H_{10} \cdot HCl$[h,j]	54	EtOH–H_2O	232–233	$C_{16}H_{19}ClN_2OS$	C, H, N
4	H	$CHOH(CH_2)_2N(CH_3)_2 \cdot 2HCl$[k]	53	EtOH	175–176	$C_{12}H_{18}Cl_2N_2OS$	N
		·Picrate		MeCN	178–179	$C_{18}H_{19}N_5O_9S$	C, H, N
5	H	$CHOH(CH_2)_2NC_5H_{10} \cdot 2HCl$[h,k]	66	EtOH–Et_2O	168–169	$C_{15}H_{22}Cl_2N_2OS$	C, H, N
		·Picrate		MeCN	167–168	$C_{21}H_{23}N_5O_9S$	C, H, N
	C_6H_5	$COCH_3$	75	C_6H_6	191–192	$C_{15}H_{11}NOS$	C, H, N
	C_6H_5	$COCH_2Br$	45	C_6H_6	192–193	$C_{15}H_{10}BrNOS$	C, H, Br
	C_6H_5	$COCH_2NC_5H_{10}$[h,l]	96	EtOH	123–125	$C_{20}H_{20}N_2OS$	C, H, N
	C_6H_5	$COCH_2N(C_2H_5)_2$[l,m]	92				
		·Picrate		EtOAc	166 dec	$C_{25}H_{23}N_5O_8S$	C, H, N
6	C_6H_5	$CHOHCH_2NC_5H_{10}$[h]	82	EtOH	152–153	$C_{20}H_{22}N_2OS$	C, H, N
7	C_6H_5	$CHOHCH_2N(C_2H_5)_2$	71	Et_2O	84–86	$C_{19}H_{22}N_2OS$	C, H, N
	C_6H_5	$CO(CH_2)_2N(CH_3)_2 \cdot HCl$[n]	81	EtOH–H_2O	234	$C_{18}H_{19}ClN_2OS$	C, H, N
	C_6H_5	$CO(CH_2)_2NC_5H_{10} \cdot HCl$[h,n]	66	EtOH–H_2O	215	$C_{21}H_{23}ClN_2OS$	C, H, N
8	C_6H_5	$CHOH(CH_2)_2N(CH_3)_2$	81	PE	110–111	$C_{18}H_{20}N_2OS$	C, H, N
	C_6H_5	$CHOH(CH_2)_2NC_5H_{10}$[h]	88	EtOH	149–150	$C_{23}H_{24}N_2OS$	C, H, N
	C_6H_5	$CHOH(CH_2)_3N(CH_3)_2$	50	PE	118–119	$C_{19}H_{22}N_2OS$	C, H, N
	CF_3	$COCH_3$	65	EtOH	104–105	$C_{10}H_6F_3NOS$	C, H, N
	CF_3	$COCH_2Br$[o]	66	EtOH	113–114	$C_{10}H_5BrF_3NOS$	C, H, Br
	CF_3	$CHOHCH_2N(C_2H_5)_2$[p]					
		·Picrate		EtOAc	164–165	$C_{20}H_{15}F_3N_5O_8S$	C, H, N
9		·1,1′-Methylenebis(2-hydroxy-3-naphthoate)[q]	68			$C_{37}H_{28}F_3N_3O_7S \cdot 2H_2O$	C, H
10	CF_3	$CHOHCH_2NC_5H_{10} \cdot HCl$[h,r]	74	EtOH	260–262	$C_{15}H_{14}ClF_3N_2OS$	C, H, N
	CF_3	$CO(CH_2)_2N(CH_3)_2 \cdot HCl$[s]	64	MeCN	180–181	$C_{12}H_{11}ClF_3N_2OS$	C, H
	CF_3	$CO(CH_2)_2NC_5H_{10} \cdot HCl$[h,s]	57	MeCN	205–206	$C_{16}H_{15}ClF_3N_2OS$	C, H
11	CF_3	$CHOH(CH_2)_2N(CH_3)_2$	69	PE	104–105	$C_{12}H_{13}F_3N_2OS$	C, H
12	CF_3	$CHOH(CH_2)_2NC_5H_{10}$[h]	85	EtOH–H_2O	126–127	$C_{16}H_{17}F_3N_2OS$	C, H
	H	$CO_2C_2H_5$[t]	55	PE	61–62	$C_{10}H_9NO_2S$	C, H
	H	CO_2H[t]		EtOH	245–246		
	H	CH_2OH	74	C_6H_6	101–105	C_8H_7NOS	C, H
	H	CHO	78	Cyclohexane–C_6H_6	92–93	C_8H_5NOS	C, H, N
	H	$CHOHCH_2NO_2$	86	EtOH	130	$C_9H_8N_2O_3S$	C, H, N
	C_6H_5	CO_2H[u]		AcOH	265	$C_{14}H_9NO_2S$	C, H
	C_6H_5	$CO_2C_2H_5$	55	EtOH	123	$C_{16}H_{13}NO_2S$	C, H
	C_6H_5	CH_2OH	91	C_6H_6	129–131	$C_{14}H_{11}NOS$	C, H
	C_6H_5	CHO	69	C_6H_6	160–162	$C_{14}H_9NOS$	C, H
	C_6H_5	$CHOHCH_2NO_2$[v]	80	EtOH	180–181	$C_{15}H_{12}N_2O_3S$	C, H, N

[a] Compounds with Arabic numerals have been tested for antimalarial activity. [b] PE = petroleum ether (bp 50–60°). [c] Resolidified at 140°, decomposed at 230–240°. [d] The ketone, R = $COCH_2NR_2$, was prepared in C_6H_6 under N_2 at 27° for 3 hr. [e] Prepared by mixing equimolar amounts of the amine·HBr and the ammonium salt of the organic acid in H_2O, filtering, and drying (P_2O_5). [f] Double mp 128–130°, 210–250° dec. [g] Prepared from the hydrobromide. [h] NC_5H_{10} = piperidino. [i] Picrate from EtOAc, mp 163–164°, was not analyzed. [j] Mannich reaction time 1 hr, separated on cooling, light yellow solid, recrystallized after charcoal treatment. [k] Base was viscous liquid; dihydrochloride was prepared in dry Et_2O. [l] Prepared in C_6H_6 at 27° for 4 hr, then at 50° for 1 hr. [m] Decomposed on heating in solvents. [n] Reaction time 12 hr; separated on cooling. [o] Prepared from the ketone and Br in AcOH at 60–70°. [p] From the bromo ketone in Et_2O at 27° for 24 hr. [q] Prepared from the crude base by the general procedure of J. H. Billman, D. G. Thomas, M. Hedrick, G. Schrotenboer, D. K. Barnes, J. Nemec, P. Trix, and E. Cleland, *J. Org. Chem.*, **11**, 773 (1964). [r] Reaction time 18 hr; separated on addition of Et_2O. [s] S. G. Fridman, *J. Gen. Chem. USSR*, **20**, 1191 (1950), gives mp 64°. [t] Lit.[7] mp 245°. [u] Lit.[7] mp 264°. [v] Prepared from aldehyde VI as described for the 2-unsubstituted derivative, but using THF instead of Et_2O.

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V. Part 5. 2-Aroxy and 2-pChloroanilino 4-quinoline Aminoalcohols

Antimalarials. 9. α-(2-Piperidyl)-4-quinolinemethanols Carrying 2-Aroxy and 2-(*p*-Chloroanilino) Groups†,[1]

Journal of Medicinal Chemistry, 16, 528 (1973).

Charles R. Wetzel,[2] James R. Shanklin, Jr.,[3] and Robert E. Lutz*

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901. *Received February 24, 1972*

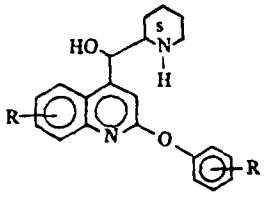
Twelve α-(2-piperidyl)-4-quinolinemethanols were synthesized from 2-chlorocinchoninic acids by additions of 2-PyLi, displacements of 2-Cl of the resulting 4-quinolyl 2-pyridyl ketones by aroxy or *p*-chloroanilino, and hydrogenations of the keto and pyridyl groups. Activities against *Plasmodium berghei* in mice were comparable with those of 2-aryl analogs. The 6,8-dichloro-2-(*p*-chlorophenoxy) compound was curative at 20 mg/kg but was phototoxic. 2-Chloro-α-diethylaminomethyl-4-quinolinemethanol, synthesized by a conventional route, was "inactive" against *P. berghei* but active against *Plasmodium gallinaceum* in birds

Syntheses of 12 α-(2-piperidyl)-4-quinolinemethanols (**1–12**) (and incidentally the 2-chlorodiethylamino alcohols **13** and **14**) were undertaken with the following expectations: that the 2-aroxy and 2-(*p*-chloroanilino) would prevent oxidative biotransformations to less active carbostyryls;[4] that these groups would lead to high activities against *Plasmodium berghei* in mice with firm binding of the molecules to the host tissues;[5] and that phototoxicity, formerly thought to be associated with conjugation of aryl and the 2-quinoline nuclei[6–8] in highly curative drugs such as **15**,[9] might be reduced by intervention between the aromatic nuclei of the heteroelement O or N which would destroy the direct conjugation although replacing it by forked conjugation.[10]

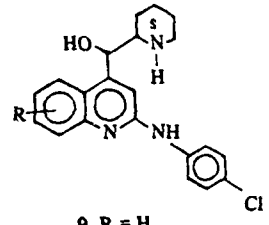
Chemistry. The α-(2-piperidyl)methanols **1–12** were synthesized from appropriate isatins through 2-hydroxy- and 2-chlorocinchoninic acids **16–20** (and ester **21**).[11–14] Rather than displacing the 2-Cl at this stage,[11] the reactions outlined in Scheme I were used, namely, additions of 2-PyLi,[15–19] then aroxy and anilino displacements of the active 2-Cl[20] of the 2-pyridyl ketones **22–26** (more difficult when an 8 substituent was present), and simultaneous Pt-H_2-AcOH[17] hydrogenations of the keto and pyridyl groups of **27–38**. Reduction of the *p*-methylthiophenoxy analog **40**, however, was incomplete and stopped at the α-(2-pyridyl)methanol stage **43**, presumably because of catalyst poisoning by sulfur of the substrate. The products **1–12** were isolated only in one of two possible racemic forms. Difficulties in and deviations from usual procedures are given in the Experimental Section.

In preliminary experiments toward making α-diethylaminomethyl-4-quinolinemethanols carrying 2-hetero substituents which might then be displaced,[20] **13** and **14** were synthesized by the standard sequence, Scheme II.[9,21]

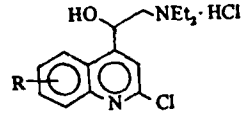
Biology. Results of tests against *P. berghei* in mice by the method of Rane[22] are given in Table I. In activities, the α-(2-piperidyl)-2-aroxy- and 2-(*p*-chloroanilino)-4-quinolinemethanols **1–12** proved to be similar to 2-aryl analogs typified by **15**.[9] That chloro is a more effective auxopharmacophore than methyl is shown by marked and consistent activity differences between analogs, and *p*-chlorophenoxy appears to be slightly more effective than *p*-chloroanilino. The most active compound was the 6,8-dichloro-2-(*p*-chlorophenoxy) (**7**); it was "active" at 10 mg/kg, curative at 20 mg/kg, and somewhat more active than the α-dibutylaminomethyl-6,8-dichloro-2-(3,4-dichlorophenyl) analog **15**. The combination of three aromatic chlorines plus the 2-aroxy oxygen in **7** has produced almost the same level of antimalarial activity as the combination of four aromatic chlorines in the α-dibutylaminomethyl 2-aryl analog **15**.



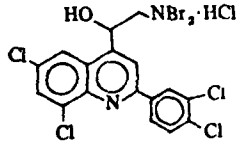
1, R = H; R′ = 4-Me
2, R = 6-Me; R′ = 4-Me
3, R = 6-Cl; R′ = 4-Me
4, R = H; R′ = 4-Cl
5, R = 6-Cl; R′ = 4-Cl
6, R = 6,8-Me_2; R′ = 4-Cl
7, R = 6,8-Cl_2; R′ = 4-Cl
8, R = 6,8-Cl_2; R′ = 3,4-Cl



9, R = H
10, R = 6-Me
11, R = 6-Cl
12, R = 6,8-Me_2



13, R = H
14, R = 6,8-Cl_2



15

Representatives of the more active of the compounds **1–12** proved to have high to moderate phototoxicities[23] comparable with those of 2-aryl and 2-aroyl analogs.[7,8,10] It appears that intervention of the hetero elements, oxygen or nitrogen, between the 2-aryl and the quinoline nuclei (like the carbonyl group in 2-aroyl analogs[10]) has little or only moderate effect on both antimalarial activity and phototoxicity.

Experimental Section

Satisfactory spectra were obtained where required for structural determination. Instruments used were: for melting point, Thomas-Hoover apparatus; ir, Perkin-Elmer 337; nmr, Hitachi Perkin-Elmer R-20; and mass spectrum, Hitachi Perkin-Elmer RMU 6E. Microanalyses by Galbraith Lab., Inc., were correct within ±0.4% (see Table II for data).

†Contribution No. 1042 of the Army Research Program on Malaria. This work was supported in part by (a) the U. S. Army Medical Research and Development Command, Office of the Surgeon General, Contract No. Da-48-193-MD-2955, R. E. Lutz, Responsible Investigator, with Postgraduate Research Assistantships to C. W. W. and J. R. S., 1968; (b) NASA Traineeship to J. R. S., 1968–1969; and (c) a fellowship to J. R. S. under A. H. Robins Co. research grant to R. E. L., University of Virginia, 1969–1970. Antimalarial and phototoxicity test results were supplied by Walter Reed Army Institute of Research (WRAIR).

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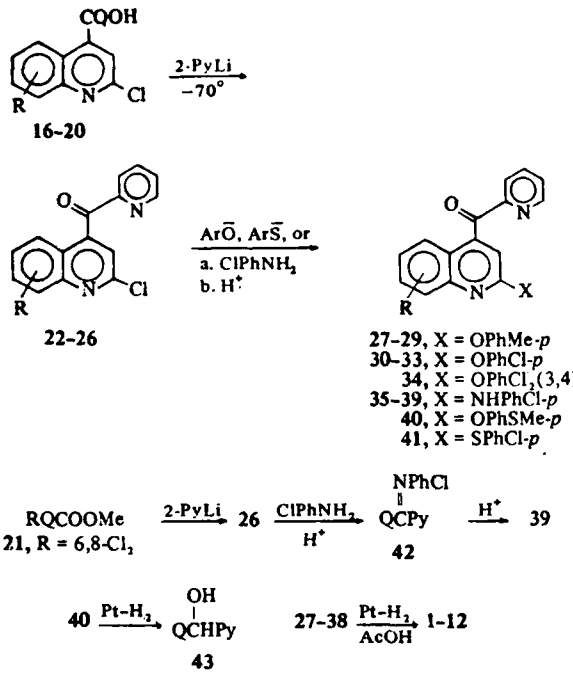
Scheme I[a]

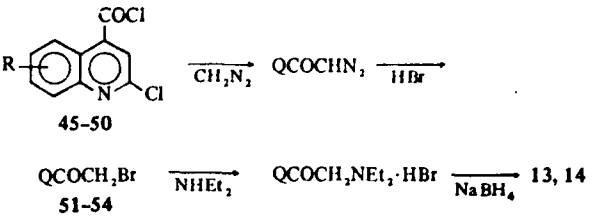


[a]Q = 4-quinolyl; R, see Table II.

2-Hydroxycinchoninic acid (75%) and derivatives, 6-Me (76%) and 7-Cl (30%), were prepared from the isatins through *N*-acetylisatin.[11,12] The derivatives, 6-Cl (51%), 6,8-Me_2 (55%), 6.8-Cl_2 (89%), and 7-Cl (65%), were made from the isatin and malonic acid (AcOH, reflux 15–17 hr).[14]

2-Chlorocinchoninic acids[12] **16–20** were obtained (*ca.* 80%) by treatment of the 2-hydroxy acids[13] with $POCl_3$ (reflux, 3 hr), hydrolysis by H_2O (3 hr; but for **17** and **20**, by solution in dioxane containing excess 2 *N* NaOH), solution in $NaHCO_3$, and reprecipitation by acid.

Scheme II



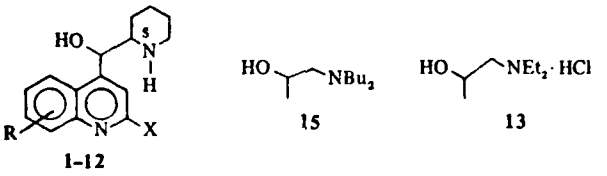
Methyl 2,6,8-Trichlorocinchoninate (21).[14] A solution of 10.8 g of 2-hydroxy-6,8-dichlorocinchoninic acid in 30 ml of $SOCl_2$, 9 ml of DMF, and 25 ml of C_6H_6 was refluxed (15 hr) and evaporated. Treatment of the residue with 5 l. of refluxing MeOH (10 min) gave **21** [ir (KBr) 1745 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.10 (s, 3, OCH_3), 7.92 (d, 1, *J* = 3 Hz, 7-H), 8.05 (s, 1, 3-H), 8.78 (d, 1, *J* = 3 Hz, 5-H)].

2-Chloro-4-quinolyl 2-Pyridyl Ketones (22–25). To 51.5 g of 22% *n*-BuLi (in hexane, 0.177 mol), in 75 ml of Et_2O (distilled from dry-Na) (−60°, under N_2, stirring), was added 28.2 g (0.179 mol) of 2-BrPy (30 min) and then 11.6 g of **17** (0.048 mol) in 450 ml of THF (distilled from $LiAlH_4$) with stirring (4.5 hr). Warming to −35°, addition of 100 ml of H_2O, H_2O quenching, standing, filtering, washing, drying (110°), and chromatography (Al_2O_3, elution with C_6H_6 and $CHCl_3$) gave **24** [ir (KBr) 1680 cm^{-1} (C=O)]. The use of Et_2O, Et_2O–THF, or THF–glyme as reaction solvent generally gave poorer yields (4% of **26**).

2,6,8-Trichloro-4-quinolyl 2-Pyridyl Ketone (26). Portionwise addition of ester **21** to 2-PyLi in Et_2O (−78°) (charcoal treatment: $CHCl_3$, Celite) gave **26** [ir (KBr) 1680 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 340 (18), 338 (54), 336 (55), 311 (36), 309 (100), 307 (100), 275 (74), 273 (100), 234 (9), 232 (32), 230 (32), 78 (78)]. A similar run in 1:1 Et_2O–THF (−60°) and chromatography (Al_2O_3, C_6H_6–CHCl) gave 4% of **26**.

2-(*p*-Methylphenoxy)-, 2-(*p*-Methylthio)phenoxy-, and 2-(*p*-Chlorophenylthio)-4-quinolyl 2-Pyridyl Ketones (27, 40, 41). A solution of 2.6 g (9.2 mmol) of **22** and 3 g of $NaOC_6H_4Me$-*p* (23 mmol) in 35 ml of dioxane (distilled from CaH_2) was refluxed (15 hr); **27** was then precipitated by H_2O quenching. **40** and **41** were made like **27** (dioxane, reflux, *ca.* 22 hr). Under similar conditions **25** was recovered (90%), and in diglyme (reflux, 6 hr) the product was an intractable oil.

Table I. Bioassay Data[a,b]



Compd	Rel no.	X	R	Antimalarial activities,[a] MST[c] (days), C (cures)[d,e] Dose, mg/kg 20	40	80	160	320	640	Phototoxicity,[b] MED,[f] Ip (oral), dose, mg/kg
1	932	OPhMe-*p*	H	0.4	0.4	0.6	0.8	0.8	1.0	
2	933	OPhMe-*p*	6-Me	0.4	0.4	0.6	0.6	2.6	7.8	
3	934	OPhMe-*p*	6-Cl	0.2	0.6	3.0	3.4	5.2	Toxic	
4	940	OPhCl-*p*	H	0.3	0.5	2.9	7.1	9.1	2C	
5	965	OPhCl-*p*	6-Cl	1.3	5.3	13.7	1C	4C	4C	75 (50)
6	945	OPhCl-*p*	6,8-Me_2	0.5	5.5	12.5	13.9	2C	2C	
7	970	OPhCl-*p*	6,8-Cl_2	2C	3C	5C	5C	5C	5C	(50)
8	973	OPhCl$_2$(3,4)	6,8-Cl_2	13.9	3C	5C	5C	5C	5C	25 (25)
9	930	NHPhCl-*p*	H	0.6	0.6	1.0	7.8	10.0	1C	
10	931	NHPhCl-*p*	6-Me	0.6	0.6	0:8	1.8	11.2	4C	15
11	938	NHPhCl-*p*	6-Cl	0.3	0.5	1.7	6.1	2C	2C	
12	939	NHPhCl-*p*	6,8-Me_2	0.3	0.3	1.7	3.7	6.9	2C	25
15[g]	556	PhCl$_2$(3,4)	6,8-Cl_2	3C[e]	6C	8C	10C	10C	10C[e]	25
13[h]	935	Cl	H		0.4	1.0	1.2	3.2		

[a]Against *P. berghei* in mice (see ref 22) [b]See ref 23. [c]Mean survival times in days; a compound is considered "active" when MST is doubled or more. [d]C = number of cures (mice surviving to 60 days) out of test groups of five mice. [e]For **15** test groups were ten mice. [f]MED = minimum effective dose in milligrams per kilogram. [g]**15** = WR 30090 (SN 15068), the 2-aryl-4-CHOHCH$_2$·HCl analog, it is included for comparison. [h]This is the α-CH_2NEt_2·HCl analog; it was active at 160 mg/kg against *P. gallinaceum* in birds.

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2-(*p*-Chlorophenoxy)-6-chloro and 6,8-Dimethyl-4-quinolyl 2-Pyridyl Ketones (31 and 32). Under the above conditions using NaOPhCl-*p* (reflux, 48 hr) **24** was recovered (80%). Use of DMSO or $DMSO_2$ as solvent (160 and 125°) gave intractable products. A solution of 1.36 g (4.5 mmol) of **25** and 4.5 g (30 mmol) of NaOPhCl-*p* in 32 g of molten *p*-chlorophenol was stirred at 95° (13 hr) and quenched in H_2O. The product, **32**, was charcoaled (Et_2O) [ir (KBr) 1685 (C=O), 1232 cm^{-1} (COC)]. Reaction of **24** under the above conditions was incomplete in 10 hr (tlc) but in 22 hr gave **31**.

2-(*p*-Chloro- and 3,4-dichlorophenoxy)-6,8-dichloro-4-quinolyl 2-Pyridyl Ketones (33 and 34). To C_6H_6-washed NaH (0.069 mol, from 3 g of a 55% dispersion in mineral oil) in 200 ml of DMF (molecular sieve 4A, 48 hr) was added dropwise a solution of 22 g (0.17 mol) of *p*-chlorophenol (in 100 ml of DMF) and then 4 g (1.32 mmol) of **26**. Heating (95°, 11 hr), H_2O quenching, and crystallization from Me_2CO (charcoal) gave **33** [ir (KBr) 1680 (C=O), 1235, 1215 cm^{-1} (COC); mass spectrum (70 eV) *m/e* (rel intensity) 432 (15.6), 430 (43.8), 428 (43.8), 326 (26.5), 324 (79), 222 (79), 78 (100)]. Compound **34** was made similarly from 3,4-dichlorophenol.

2-(*p*-Chloroanilino)-4-quinolyl 2-Pyridyl Ketones (35-38). A 50-ml solution of 3.5 g (0.0118 mol) of **25** and 6 g of *p*-chloroaniline in absolute EtOH was refluxed (48 hr; **23** and **24** required only 6 hr). After adding 50 ml of H_2O and 25 ml of concentrated HCl, and again refluxing (1 hr), **38** was precipitated by H_2O–NaOH quenching [ir (KBr) 1720 cm^{-1} (C=O)]. Without HCl the anil was obtained, mp 198–200° (not analyzed) [ir (KBr) 1630 cm^{-1} (C=N)]. The 2,6-Cl_2 ketone **26** under these conditons failed to react with 2,4-dimethylaniline (24 hr).

2-(*p*-Chloroanilino)-6,8-dichloro-4-quinolyl 2-Pyridyl Ketone (39) and Its Anil (42). A solution of 5.9 g (17.6 mmol) of **26** and 5.1 g of *p*-chloroaniline·HCl in 100 ml of *p*-chloroaniline was stirred at 95° (under N_2, 8 hr). H_2O quenching gave **42**. Solution in 1.8 l. of 1.5 *M* HCl in 60% EtOH and refluxing (2 hr) gave **39**. In a separate experiment, anil **42** was washed with dilute NaOH [ir (KBr) 1685 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 431 (36), 429 (98), 427 (100), 325 (20), 323 (59), 321 (59), 290 (8), 288 (27), 286 (34), 78 (61)]. It is evident that displacement of 2-Cl by an aniline is impeded by an 8-quinoline substituent and by *o*-Me in the aniline and that the reaction is autocatalyzed by HCl liberated.[24]

2-Aroxy- and 2-(*p*-Chloroanilino)-α-(2-piperidyl)-4-quinolinemethanols (1-12). Hydrogenations of the 2-pyridyl ketones **27-39** were by Pt-H_2 (0.2 g of 84% PtO_2 per 3 g of substrate at 43 psi in 250 ml of AcOH), followed by filtration (Celite), and NaOH–H_2O quenching (directly or after vacuum evaporation of AcOH and solution in Me_2CO).

α-(2-Pyridyl)-2-[*p*-(methylthio)phenoxy]-4-quinolinemethanol (48) was made from **40** by Pt-H_2-AcOH (as above) [ir (KBr) 3100 cm^{-1} (broad, OH); nmr ($CDCl_3$) δ 2.50 (s, 3, SCH_3), 4.40 (s, 1, OH), 6.42 (s, 1, *CHOH*)].

Attempted Synthesis of α-(2-Piperidyl)-6,8-dichloro-2-(*p*-chlorophenyl)-4-quinolinemethylamine (QCH(NH_2)Pip; for Comparison with 7 and 15). 6,8-Dichloro-2-(*p*-chlorophenyl)-4-quinolyl 2-Pyridyl Ketoxime, QC(2-Pip)=NOH (44). Reaction of 2-PyLi–Et_2O with the cinchoninic methyl ester (−78°, under N_2) and treatment of the resulting ketone (83%) with NH_2OH·HCl–pyridine in absolute EtOH (reflux 6 hr) gave **44** [ir (KBr) 3225 cm^{-1} (*OH*), no C=O band]. Pt-H_2-AcOH reduction[25] gave an unpromising mixture (six compounds, tlc).

2-Chlorocinchoninyl Chlorides (45-50). For **45** and **48**, see ref 13. For the others, a melt of 69 g (0.278 mol) of (*e.g.*) **20** and 112 g (0.535 mol) of PCl_5 was refluxed (5 hr), cooled, washed (Et_2O), and charcoaled (hot C_6H_6).

2-Chloro-4-quinolyl Bromomethyl Ketones (51-54). Addition of **49** (11.3 g, 0.05 mol) to 6 g (0.14 mol) of CH_2N_2 in 400 ml of alcohol-free Et_2O (4 hr), addition of 40 ml of 48% HBr (1 hr), extractions (Et_2O), drying ($CaSO_4$), and evaporation gave **53**.

2-Chloro-α-diethylaminomethyl-4-quinolinemethanols (13, 14). To a solution of 2.84 g (0.01 mol) of (*e.g.*) **51** in 51 ml of Et_2O was added 2.82 g of Et_2NH (3 hr, 20°). After filtration and vacuum evaporation, a solution of the oil in 50 ml of MeOH was treated with 0.35 g of $NaBH_4$[21] and 4 ml of H_2O (stirring 3 hr). After quenching (1.5 l. of H_2O, standing 5 hr), vacuum evaporation of Et_2O extracts, solution of the residue in Et_2O and drying ($CaSO_4$), **13**·HCl was precipitated by dry HCl-Et_2O.

2-Chloro-4-cyanoquinolines (55-60).[26,27] The 2-chlorocinchoninic acids (where attempts at direct KF exchange had failed) were converted to acid chlorides **45-50** and thence by C_6H_6-NH_3-H_2O (stirring) to crude amides (air-dried) which were then treated (16 hr) with refluxing $POCl_3$-PCl_5 (rather than $SOCl_2$).

2-Hydroxy-4-acetylquinoline (61). Reaction of 2-chloro-4-cyanoquinoline (**55**) with MeLi (−60°, Et_2O, 3 hr) was incomplete. After recovery of **55** (38%) and hydrolysis of the EtOH filtrate, an equal volume of 18% HCl was added (reflux, 2 hr), giving **61**.

2-Fluoro-4-cyanoquinolines[26] (62-66). With KF in DMSO (anhydrous, under N_2, 180°), **55-60** underwent selective displacement of 2-Cl by F. Attempted hydrolysis of CN of **62** (75%, H_2SO_4, 100°, 4 hr) gave 2-hydroxycinchoninic acid, whereas under these conditions 2-chloronitrile **55** was converted into 2-chlorocinchoninic acid (**16**).

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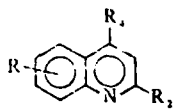
Table II. Quinoline Compounds[a]



Compd	R	R_1	R_4	Crystn solvent[b-l]	Mp, °C	% yield	Formula	Analyses[m-p]
1	H	OPhMe-*p*	CHOHPip	EtOH	199–200	61	$C_{22}H_{24}N_2O_2$	C, H, N
2	6-Me	OPhMe-*p*	CHOHPip	EtOH	167–169	38	$C_{23}H_{26}N_2O_2$	C, H, N
3	6-Cl	OPhMe-*p*	CHOHPip	EtOH	180–181	46	$C_{22}H_{23}ClN_2O_2$	C, H, N
4	H	OPhCl-*p*	CHOHPip	EtOH	173–174	42	$C_{21}H_{21}ClN_2O_2$	C, H, N
5	6-Cl	OPhCl-*p*	CHOHPip	EtOH	183.5–185	40	$C_{21}H_{20}Cl_2N_2O_2$	C, H, N
6	6,8-Me_2	OPhCl-*p*	CHOHPip	EtOH	171–172	52	$C_{23}H_{25}ClN_2O_2$	C, H, N
7	6,8-Cl_2	OPhCl-*p*	CHOHPip	*h*	208–209 dec	42	$C_{21}H_{19}Cl_3N_2O_2$	C, H, N
8	6,8-Cl_2	OPhCl$_2$(3,4)	CHOHPip	Me_2CO[i]	196–198 dec	51	$C_{21}H_{18}Cl_4N_2O_2$	C, H, N, Cl
9	H	NHPhCl-*p*	CHOHPip	EtOH–H_2O[j]	183–185		$C_{21}H_{22}ClN_3O$	C, H, N
9·H_2O				EtOH–H_2O	131–133	87	$C_{21}H_{22}ClN_3O \cdot H_2O$	C, H, N
10	6-Me	NHPhCl-*p*	CHOHPip	EtOH–H_2O[j]	117–119	89	$C_{22}H_{24}ClN_3O$	C, H, N
11	6-Cl	NHPhCl-*p*	CHOHPip	*j*	185–187		$C_{21}H_{21}Cl_2N_3O$	C, H
11·H_2O					115–117		$C_{21}H_{21}Cl_2N_3O \cdot H_2O$	C, H, N
12	6,8-Me_2	NHPhCl-*p*	CHOHPip	EtOH–H_2O[j]	228–229	63	$C_{23}H_{26}ClN_3O$	C, H
13	H	Cl	CHOHCH$_2$NEt$_2$·HCl	EtOH–Et_2O	204–205	15	$C_{15}H_{19}ClN_2O \cdot HCl$	C, H, N
14	6,8-Cl_2	Cl	CHOHCH$_2$NEt$_2$·HCl	*k*	96–99	40	$C_{15}H_{17}Cl_3N_2O \cdot HCl$	C, H[n]
16	6-Me	Cl	COOH	*b*	195 dec		$C_{11}H_8ClNO_2$	C, H
17	6-Cl	Cl	COOH	*b*	187 dec		$C_{10}H_5Cl_2NO_2$	C, H
18	7-Cl	Cl	COOH	*b*	206 dec		$C_{10}H_5Cl_2NO_2$	C, H
19	6,8-Me_2	Cl	COOH	*b*	205 dec		$C_{12}H_{10}ClNO_2$	C, H
20	6,8-Cl_2	Cl	COOH	*b*	250–253 dec		$C_{10}H_4Cl_3NO_2$	C, H
21	6,8-Cl_2	Cl	COOMe	MeOH	167–169		$C_{11}H_6Cl_3NO_2$	C, H
22	H	Cl	COPy	EtOH	149–150	69	$C_{15}H_9ClN_2O$	C, H, N
23	6-Me	Cl	COPy	EtOH	154.5–155.5	68	$C_{16}H_{11}ClN_2O$	C, H
24	6-Cl	Cl	COPy	*d*	203–204.5	54	$C_{15}H_8Cl_2N_2O$	C, H
25	6,8-Me_2	Cl	COPy	EtOH	168–169	74	$C_{17}H_{13}ClN_2O$	C, H
26	6,8-Cl_2	Cl	COPy	EtOH	212–214	68	$C_{15}H_7Cl_3N_2O$	C, H
27	H	OPhMe-*p*	COPy	EtOH	136–137.5	71	$C_{22}H_{18}N_2O_2$	C, H
28	6-Me	OPhMe-*p*	COPy	EtOH	111–112.5	82	$C_{23}H_{18}N_2O_2$	C, H
29	6-Cl	OPhMe-*p*	COPy	EtOH	87–89	35	$C_{22}H_{15}ClN_2O_2$	C, H
30	H	OPhCl-*p*	COPy	EtOH	151–153	40	$C_{21}H_{13}ClN_2O_2$	C, H
31	6-Cl	OPhCl-*p*	COPy	Me_2CO–$CHCl_3$	163.5–165	71	$C_{21}H_{12}Cl_2N_2O_2$	C, H, N, Cl
32	6,8-Me_2	OPhCl-*p*	COPy	EtOH	134–135	73	$C_{23}H_{17}ClN_2O_2$	C, H, N
33	6,8-Cl_2	OPhCl-*p*	COPy	Me_2CO	207–208	80	$C_{21}H_{11}Cl_3N_2O_2$	C, H, N
34	6,8-Cl_2	OPhCl$_2$(3,4)	COPy	EtOH[e,f]	222–223 dec	52	$C_{21}H_{10}Cl_4N_2O_2$	C, H, N, Cl
35	H	NHPhCl-*p*	COPy	EtOH	182–184	83	$C_{21}H_{14}ClN_3O$	C, H
36	6-Me	NHPhCl-*p*	COPy	EtOH	180–182	56	$C_{22}H_{16}ClN_3O$	C, H
37	6-Cl	NHPhCl-*p*	COPy	EtOH	212–213	45	$C_{21}H_{13}Cl_2N_3O$	C, H
38	6,8-Me_2	NHPhCl-*p*	COPy	EtOH	208–209.5	79	$C_{23}H_{18}ClN_3O$	C, H
39	6,8-Cl_2	NHPhCl-*p*	COPy	EtOH[g]	236–237 dec	78	$C_{21}H_{12}Cl_3N_3O$	C, H, N
40	H	OPhSMe-*p*	COPy	Me_2CO	174.5–176	61	$C_{22}H_{16}N_2O_2S$	C, H, N
41	H	SPhCl-*p*	COPy		149.5–151		$C_{21}H_{13}ClN_2OS$	C, H[o]
42	6,8-Cl_2	NHPhCl-*p*	C(Py)=NPhCl-*p*	$CHCl_3$–hexane	165–170[l]		$C_{27}H_{16}Cl_4N_4$	C, H, N
43	H	OPhSMe-*p*	CHOHPy		140–142	71	$C_{22}H_{18}N_2O_2S$	C, H, N
44	6,8-Cl_2	PhCl-*p*	C(Pip)=NOH		264–265.5	58	$C_{21}H_{12}Cl_3N_3O$	C, H, N
45	H	Cl	COCl	C_6H_6[c]	95		$C_{10}H_5Cl_2NO_2$	*q*
46	6-Me	Cl	COCl	C_6H_6[c]	125–126.5		$C_{11}H_7Cl_2NO$	C, H
47	6-Cl	Cl	COCl	C_6H_6[c]	128–129.5		$C_{10}H_4Cl_3NO$	C, H
48	7-Cl	Cl	COCl	C_6H_6[c]	106–107.5		$C_{10}H_4Cl_3NO$	C, H
49	6,8-Me_2	Cl	COCl	C_6H_6[c]	94.5–96	49	$C_{12}H_9Cl_2NO$	C, H
50	6,8-Cl_2	Cl	COCl	C_6H_6[c]	109–110	71	$C_{10}H_3Cl_4NO$	C, H
51	H	Cl	COCH$_2$Br	EtOH	101–102	86	$C_{11}H_8BrClNO$	C, H
52	6-Me	Cl	COCH$_2$Br	EtOH	97–98	80	$C_{12}H_{10}BrClNO$	C, H
53	6,8-Me_2	Cl	COCH$_2$Br	EtOH	71–72.5	73	$C_{13}H_{11}BrClNO$	C, H
54	6,8-Cl_2	Cl	COCH$_2$Br	EtOH	98–98	77	$C_{11}H_5BrCl_3NO$	C, H[p]
55	H	Cl	CN	EtOH	153–154	78	$C_{10}H_5ClN_2$	C, H
56	6-Me	Cl	CN	EtOH	121–122	55	$C_{11}H_7ClN_2$	C, H
57	6-Cl	Cl	CN	EtOH	178–179.5	63	$C_{10}H_4Cl_2N_2$	C, H
58	7-Cl	Cl	CN	EtOH	145–147	47	$C_{10}H_4Cl_2N_2$	C, H
59	6,8-Me_2	Cl	CN	EtOH	153–154	64	$C_{12}H_9ClN_2$	C, H
60	6,8-Cl_2	Cl	CN	EtOH	174–175	78	$C_{10}H_3Cl_3N_2$	C, H
61[r]	H	OH	COMe	EtOH	199–200	60	$C_{11}H_9NO_2$	C, H
62	H	F	CN	EtOH	141–141.5[c]	67	$C_{10}H_5FN_2$[c]	C, H, N
63	6-Me	F	CN	EtOH	121–122[c]	63	$C_{11}H_7FN_2$[c]	C, H, F
64	6-Cl	F	CN	EtOH	182–183.5[c]	49	$C_{10}H_4ClFN_2$[c]	C, H, F
65	6,8-Me_2	F	CN	EtOH	125–126[c]	43	$C_{12}H_9FN_2$[c]	C, H, N
66	6,8-Cl_2	F	CN	EtOH	155–156[c]	54	$C_{10}H_3Cl_2FN_2$[c]	C, H, F

[a]Py = 2-pyridyl; Pip = 2-piperidyl; Ph = phenyl. [b]Partial purification by solution in $NaHCO_3$ and precipitation by HCl, oven dried. [c]Vacuum sublimed. [d]Chromatography; Al_2O_3, C_6H_6–$CHCl_3$. [e]Chromatography; Florisil, $CHCl_3$. [f]Chromatography; Florisil, $CHCl_3$–hexane. [g]EtOH–$CHCl_3$. [h]Me_2CO–CH_2Cl_2 or CH_2Cl_2 (entrapment of C_6H_6 or Me_2CO shown by nmr); dried at 100° (0.05 mm) (48 hr) or crystallized from CH_2Cl_2. [i]Crystallization from Me_2CO rapidly gave polymorph A; crystallization slowly gave polymorph B with the same melting point and nmr ($CDCl_3$) but differing in the ir (KBr) fingerprint region, the ir (KBr) of A after solution in $CHCl_3$ and evaporation over KBr was identical with that of B (KBr). [j]Vacuum dried (100°). [k]Sample not recrystallized. [l]Solidified at 175°; remelted at 261.5–263°. [m]Analyses were within ±0.4% of theory except as follows. [n]C: calcd, 46.90; found, 47.40. [o]H: calcd, 3.48; found, 3.85. [p]C: calcd, 37.39; found, 38.15 (sample not recrystallized). [q] [r]

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Part 6. 3-Substituted-2-aryl-4-quinoline Aminoalcohols.

Antimalarials. 10. 3-Substituted α-Dialkylaminomethyl-2-aryl-4-quinolinemethanols.[#1]

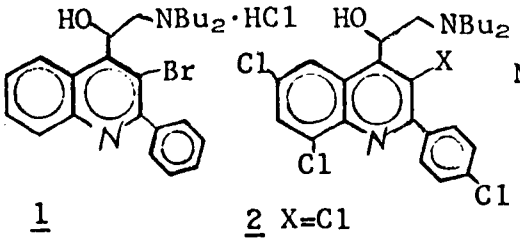
Manuscript which will be submitted for publication in the Journal of Medicinal Chemistry

H. R. Munson, Jr.,* R. E. Johnson, J. M. Sanders, C. J. Ohnmacht and R. E. Lutz*

Department of Chemistry, University of Virginia
Charlottesville, Virginia 22901

Abstract 4',6,8-Trichloro-2-phenyl-4-quinoline aminoalcohols with a fourth group in the 3-position, Cl, F or OMe, were synthesized for antimalarial tests. A new modification of the Pfitzinger reaction was successful with α-haloacetophenones, utilizing methoxyethanol and trace amounts of KOH. The 3-halo aminoalcohols were made *via* diazomethylation of the acid chlorides; and the OMe derivative was made *via* the 4-quinaldehyde and methylenation. The 3,4',6,8-Cl_4 and 3-F-4',6,8-Cl_3 compounds were curative against *Plasmodium berghei* in mice at 10-40 mg/kg; they were moderately phototoxic in animals.

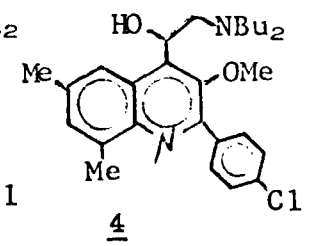
3-Halo and 3-methoxy 2-aryl-4-quinoline aminoalcohols 1-4 were synthesized for comparison with the highly curative antimalarial 7[2a], to gain further information concerning earlier indications that phototoxicity in 2-aryl types paralleled electronegativities of 4'-substituents[3], $Cl > CH_3 > OCH_3$, and is decreased by the combination of 3-Me and 2'-Cl which must sterically interfere with coplanarity and effectiveness of conjugation of the π-systems[3] (eg 5,8,9[4]). This work when started was given impetus by the postulate that phototoxicity of a final drug might be anticipated from phototoxicity of the cinchophen from which it was made, and from the finding that 3-bromocinchophen (11) was not phototoxic. However, this factor *per se* now seems inconsequential in light of the effectiveness of 7[2a] for treatment of acute malarial in clinical trials on man[2b,c] where photosensitivity proved to be a minor consideration.



1

2 X=Cl

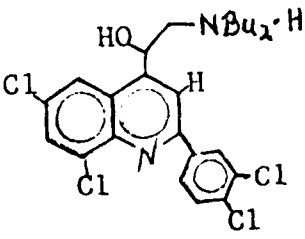
3 X=F



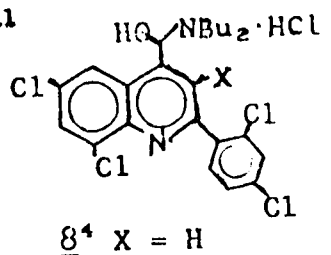
4

5[4]·HCl X = Me

6[2a] X=H



7[2a]



8[4] X = H

9[4] X = Me

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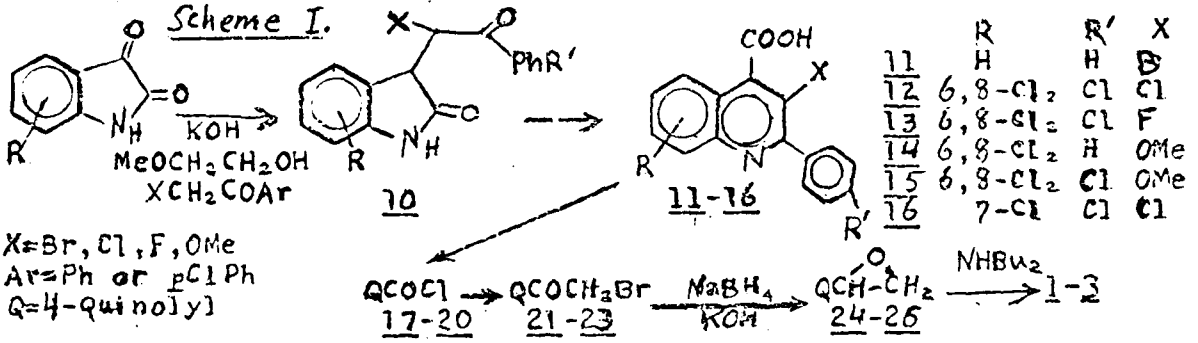
Chemistry

Attempted addition of 2-PyLi[5] to 3-bromocinchophen (11[e]) having failed, aminoalcohol 1 was synthesized by the classical route[2a] outlined in Scheme 1: diazomethylation of the acid chloride 17, hydrobromination of the diazoketone, $NaBH_4$-KOH reduction of bromoketone 21 to the epoxide 24, and condensation with $NHBu_2$.

Attempts to make intermediate cinchophens 12 and 13 from the isatin and the highly reactive 2-haloacetophenones by modified[7] Pfitzinger procedure were unsuccessful, but 3-methoxycinchophens 14 and 15 were obtainable by this method[7c,d] using the less reactive α-methoxyacetophenones. A new procedure was then developed for the reaction with α-haloacetophenones using methoxyethanol as solvent with smaller amounts of KOH, which gave 3-halocinchophens 11-13 in good yields. Since neither 12 nor its Me-ester reacted with 2-PyLi under the usual conditions[5], the 3-halo cinchophens 12 and 13 were converted into aminoalcohols 2 and 3 by the classical route[2] as illustrated in Scheme I.

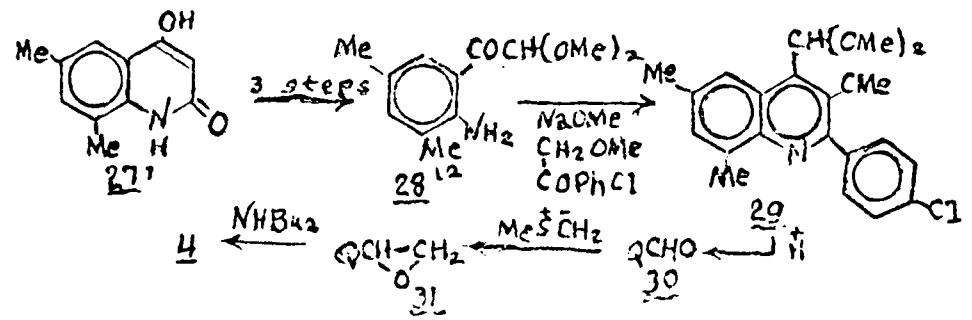
Scheme I.



	R	R′	X
11	H	H	Br
12	6,8-Cl2	Cl	Cl
13	6,8-Cl2	Cl	F
14	6,8-Cl2	H	OMe
15	6,8-Cl2	Cl	OMe
16	7-Cl	Cl	Cl

Diazomethylation of 3-methoxy-6,8-dichlorocinchophen acid chloride (20) and hydrobromination failed to give the desired bromomethyl ketone (loss of 3-OMe was shown by ir). A synthetic approach[8] through the 4-hydroxycarbostyryl to 4-quinaldehyde[9] was then successfully applied to make compound 4, as outlined in Scheme II, starting from 6,8-dimethyl-4-hydroxycarbostyryl (27), chosen instead of the preferred 6,8-Cl_2 analog where reported yields were low[9c]. This involved conversion into the 2-amino glyoxal acetal 28, condensation with $MeOCH_2COPhCl_p$, hydrolysis of 29 to 4-quinaldehyde 30, methylenation[10] to epoxide 31, and condensation with $NHBu_2$ to 4.

Scheme II.



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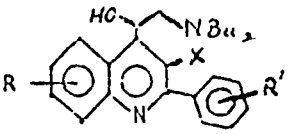
Antimalarial Activities. Table I includes test results against P. berghei in mice (method of Rane[11]) and photoxicities[3], on four new 3-substituted 4-quinoline aminoalcohols 1-4, and also on 5-9[2,4] for comparisons. Of 1-4, the 3-fluoro derivative 3 was the most active (at 2.5 mg/kg) and curative at 10 mg/kg .

TABLE I.

Antimalarial Activities[a] Against P. berghei in Mice



Cpd.	WR No.	Substituents R	R'	X	IMST (days)[b], C (cures)[c,d] Dose, mg/kg 10	20	40	80	160	320	Phototoxicity[e] MED[f] (mice) ip, mg/kg
2	140089	6,8-Cl_2	4-Cl	Cl	6.4	8.2	1C	3C	3C	5C	50
3	149105	6,8-Cl_2	4-Cl	F	1C	2C	3C	5C	5C	5C	100
4	157307	6,8-Me_2	4-Cl	OMe	0.7	4.1	6.1	8.1	14.1	4C	100
5[g]	42934	6,8-Cl_2	4-Cl	Me	7.2	10.6	1C	2C	2C	2C	12.5
6[h]	29252	6,8-Cl_2	4-Cl	H	2C	3C	4C	5C	5C	5C	25
6A[h]	28616	6,8-Me_2	4-Cl	H	5.9	10.1	2C	4C	4C	5C	-
7[h]	30090	6,8-Cl_2	3,4-Cl_2	H	15	3C	6C	8C	10C	10C	50
8[g]	53188	6,8-Cl_2	2,4-Cl_2	H	1.0	3.5	9.1	2C	3C	4C	12.5
9[g]	63489	6,8-Cl_2	2,4-Cl_2	Me	0.3	1.3	1.7	7.1	1C	2C	100
1	121473	H	H	Br		0.1		0.1		0.3	Neg

[a]See ref. 11. [b]IMST=Increase in mean survival time in days; cpd. considered active when IMST is at least twice that of controls (6 days). [c]C= Number of cures (mice surviving 60 days) of test groups of five mice. [d]Test groups for 7 were ten mice. [e]Ref. 3. [f]MED = Min. effective dose. [g]Ref. 4. [h]Ref. 2a.

The results for the 6,8-dichloro-2-(p-chlorophenyl) and dichlorophenyl compounds, 2,3,5,6 and 7,8,9, show that as the bulk of the 3-substituent increases (H<F<Cl<Me) the antimalarial activities decrease in that order, 6>3>2>5 and 7>>8>9, paralleling the Taft steric parameter E_s (Table II) which has been used by Hansch[12] in quantitative multiparameter structure-activity correlations. The relationship can be seen at 10-20 mg/kg and is more pronounced at 40-80 mg/kg. Activity decreases as E_s becomes more negative. The same effect is observed for the isomeric 2-(dichlorophenyl) series 7-9 and 2 with regard to the ortho position in the 2-phenyl ring. A comparison of the activities of 2 and 8 shows that the 3 and 2'-positions are similar in effect for Cl as substituent. One explanation for this is that inhibition of coplanarity of the 2-phenyl and quinoline rings reduces antimalarial activity.

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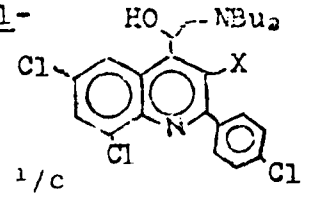
Table II. Structure-Activity Parameters for 3-X-2-Aryl-4-quinolinemethanols Against P. berghei in Mice.



$$\log 1/c = 0.661\ (\pm 0.34)E_s - 3 + 0.824(\pm 0.25)$$

n r s
5 0.962 0.104

cpd	X	E_s	π	σm	σp	MR	MW	log 1/c o sd.	log 1/c calc.	Δ log 1/c
6	H	1.24	0	0	0	1.03	1	1.641	1.644	-0.003
3	F	0.78	0.10	0.34	0.06	0.92	19	1.462	1.340	0.122
4[b]	OMe	0.69	-0.33	0.12	-0.27	7.87	31	1.165[b]	1.280	-0.115
2	Cl	0.27	0.59	0.37	0.23	6.03	35	0.955	1.003	-0.048
5	Me	0	0.68	-0.07	0.17	5.65	15	0.867	0.824	0.043

[a]Calcd. using equation. [b]Values calcd. for 6,8-Cl_2 analog (3.7x6A).

Recently Hansch and Craig[13] reported on the antimalarial structure-activity relationships for a series of phenanthrene amino-alcohols as determined by multiple parameter analysis and by additivity methods; and Craig[14] reported on the Free-Wilson analysis of 2-phenyl-quinoline-4-aminoalcohols. It was concluded that both 1-octano-water partition coefficients (π) and electronic parameters (σ) could account for most of the biological variation for members of these series. For the quinoline series, the relative magnitude of these factors were separated according to functional group and position[14]. When the nature and position of all other substituents are held constant for the 3-X-phenylquinoline system, the steric effect of the 3-substituent for compounds 2-6 can be expressed by the equation in Table II using the method described by Hansch[15]. This is the best single paremeter equation ($F_{1,3} = 37.2$, $F_{1,3,\alpha 0.01} = 34.1$) for the limited set of compounds.

The methoxy derivitive 4 which carries 6,8-dimethyl rather than the preferred 6,8-dichloro , has considerably lower antimalarial activity than expected for the steric effect of the methoxyl group alone. Obviously this is because 6,8-dichloro is a much better auxopharmacophoric combination than 6,8-dimethyl[14]. e.g. Comparison of ED_{50} values for increase in mean survival times (P. berghei in mice) by the 6,8-dichloro compound 6 with those of the 6,8-dimethyl analog 6A, shows the former to be 3.7 times more potent . And the 2-p-chlorophenoxy analog of 6,8-dichloro compound 6 is 5 times as active as the 6,8-dimethyl analog[16].

No relationship is obvious between planarity of the total π system and animal phototoxicities for any of the analogs except 5, 8 and 9 (cf. discussion by Rothe and Jacobs[3a]). Recent results from clinical trials[2b-e] with 7 has cast considerable doubt on the correlatability of phototoxicity in animal models with that shown in man, as 7 was shown to be both prophylactic and effectively curative[2d] for acute malaria caused by several strains of P. falciparum with no observed adverse side effects and phototoxicity a minor consideration[11].

Compound 7 and the new isomer 2 have equal phototoxicities in animals, but 2 has half the antimalarial activity of 7. The 3-fluoro compound 3, on the other hand, is considerably more active than 7 against P. berghei and half as phototoxic; it therefore appears to be a better candidate than was 7 for clinical trial in ...

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Experimental Section[6]

4- and 6-Chloroisatins[17] were prepared from isonitroso-3-chloro-acetanilide, cyclizing in concd H_2SO_4 (80°), and separating by fractional precipitation by H+.

2-Methoxy-4'-chloroacetophenone[15]. Mp 65-66°; nmr ($CDCl_3$) δ, 3.15 (s,3), 4.69 (s,2), 7.35-8.10 (m,4).

New Modification of the Pfitzinger Reaction. 3,4',6,8-Tetrachlorocinchophen (12) (13 made similarily).- To a suspension of 21.6 g (0.1 mol) of 5,7-dichloroisatin and 18.9 g (0.1 mol) of α,4'-dichloroacetophenone in 2-methoxyethanol (300 ml, stirred, 10 min) was added KOH (48 mg, stirring, 18 hr). Slow addition of concd HCl (250 ml) followed by EtOH (to suspend the precipitate), cooling (30°), basification (to pH 11, 10% NaOH), filtration, and acidification (to pH 3, 10% HCl), gave 12 (25.3 g, 65%), mp 245-250° dec. Use of 2-propanol or DMF-EtOH mixture gave 12-25% of 12; and use of $MeOCH_2CH_2OH$ gave 65% (10% unreacted) and a very low yield of 14.

3-Methoxy-6,8-dichlorocinchophen (14)(cf. ref 7). Nmr (Me_2CO-d_6): δ 3.71 (s,3,CH_3), 6.96 (broad s, conc dependent, 1, COOH), 7.83 (m,7,aromatic).

The 2-Arylquinoline-4-carbonyl Chlorides 17-20[16] were made from 11-14 by excess $SOCl_2$ (1-1.5 g/10 ml, reflux 2-3 hr), distilling and coevaporating with benzene to remove $SOCl_2$, solution of product in hot CH_2Cl_2, filtration (Celite), evaporation and cooling.

3-Fluoro-6,8-dichloro-2-(4'-chlorophenyl)-4-quinolyl Bromomethyl Ketone (23) (21 and 22 were made similarly).- To stirred 350 ml of Et_2O-CH_2N_2 (0.7 mol) was added 5.6 g (0.014

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mol) of 19 (18 hr), and then 20 ml of concd HBr (3 hr). Washing the Et_2O solution (H_2O), drying ($MgSO_4$), evaporation, and slurrying the residue (petroleum ether, 30-60°), gave 5.64 g (87%), mp 153-163° dec. [In the case of 22 Et_2O-CH_2N_2 was added to 18 in CH_2Cl_2 (stirring, 0°)]. After workup by solution in Me_2CO, evaporation, trituration with MeOH, and crystallization from Me_2CO, the product gave unsatisfactory analysis and was shown to contain at least one important minor compd (tlc, benzene-MeOH); however, spectra showed that the bulk of the mixture was 23, which in the next step gave 26.

3,6,8-Trichloro-2-(4'-chlorophenyl)-4-quinoline Ethylene Oxide (25) (26 and 31 were made similarly). To a soln of 22 (3 g, 6.46 mmol) in 50 ml of THF was added a soln of 1.25 g (3.30 mmol) of $NaBH_4$ in 14.5 ml of 3% KOH-H_2O, followed by addn of 40 ml of THF and 20 ml of EtOH to effect soln (stirred 1 hr); 25 (2.1 g) precipitated.

α-(Di-n-butylaminomethyl)-3,6,8-trichloro-2-(4'-chlorophenyl)-4-quinolinemethanol (2) (3 was made similarly). A mixture of 3.2 g (8.27 mmol) of 25 and 6 ml of $NHBu_2$ was heated (stirring, 17 hr, 132°), vac evaporated in vacuo to remove $NHBu_2$ (80°). Trituration with hexane and cooling gave 2 (4 g).

3-Bromo-α-(di-n-butylaminomethyl)-2-phenyl-4-quinolinemethanol·2 HCl (1). Solution of 21 (2 g, 5 mmol) and $NHBu_2$ (1.3 g, 10 mmol) in Et_2O (standing, dark, room temperature, 8 hr), filtration (removing 6.2 g (94%) of $NHBu_2$·HBr), vacuum evaporation (70°), solution of the residue (EtOH, under N_2), addition of $NaBH_4$ (15 g, 39.5 mmol), stirring (0.5 hr), basification (dil NaOH, to pH 11), extraction with Et_2O, drying ($MgSO_4$), vacuum evaporation, solution in dry Et_2O, and addition of Et_2O-HCl, gave 1 (0.5 g).

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3-Methoxy-6,8-dimethyl-2-(4'-chlorophenyl)-4-quinaldehyde Dimethyl Acetal (29). A sol'n of $MeOCH_2COPhCl_p$ (4.3 g) and 27 (5.18 g; MeOH, 40 ml), was added rapidly to a stirred MeOH solution of 0.57 g of Na (30 ml). Refluxing (4.5 hr, precipitate appeared after 3.5 hr), cooling (-5°), filtration, and washing (MeOH, 0°), gave 29 (7.88 g including recovery from filtrate).

3-Methoxy-6,8-dimethyl-2-(4'-chlorophenyl)-4-quinaldehyde (30). A solution of 29 (5 g) in 5:1 dioxane-H_2O (60 ml) plus 1 ml of conc HCl, was refluxed (35 min). Addition of H_2O (40 ml) and cooling (5°) gave 30 (4.27 g). Epoxide 31 was made from 30 by methylenation[10] and converted into aminoalcohol 4 by $NHBu_2$ (3.5 hr, 145-150° and 14 hr, 110°).

Toward a New Synthesis of 3-Substituted-2-phenyl-4-quinoline Aminoalcohols (Scheme III). The Schmidt reaction on α,β-dibromo-cis-chalcone (32) gave 3,4-dibromo-2-phenylquinoline (33[17]). From a quantity of 33 prepared by the Kaslow bromination procedures, 34 → 35 → 33[18], a small amount of tribromide 36 was isolated, which became the predominant product of bromination by $POBr_3$ in DMF. The reaction of 3,4-dibromo-2-phenylquinoline (33) with CuCN-DMF (reflux) gave a difficultly separable mixture which was shown by mass spectrum to be mono and 3,4-di-nitriles 37 and 38 in a ratio dependent on reaction time (57/43 after 1 hr and 36/64 after 4 hr). Obviously the 3-Br, relatively inactive in 33, is activated in 37 by the 4-CN. Use of highly polar DMF as solvent for $POBr_3$ brominations, and displacements of 4-Br by CN, thus appear to be potentially useful. There is the possibility for selective 4-metalation of 33 by BuLi and subsequent reaction with CO_2 or 2-pyridaldehyde, or reaction at the 4-CN of 37, for creation of the aminoalcohol chain. A start was made toward synthesis of the 3,4',7-trichloro analog of 2, from cis $pClPhCCl{=}CClCOPhCl_p$.[19]

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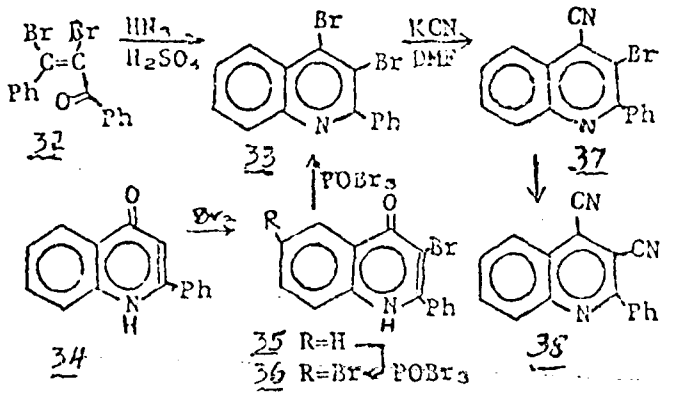
Scheme III



Acknowledgment. Because only test data on 5, 8 and 9 have been published, chemical data by J. Riedmaier and J. Christensen are included here with their permission.[4] We are grateful to Dr. S. W. Page (WRAIR) for providing the biological data, and to Mrs. E. Zacharias (A. H. Robins Co.) for programming assistance.

Footnotes and References

#Contribution No. of the Army Research Program on Malarial. Work initiated under a University of Virginia Teaching Assistantship (R. E. J.). Supported: (a)in large part by the U. S. Army Medical Research and Development Command, Office of the Surgeon General, Contract No. Da-48-193-MD-2955, R. E. Lutz, Responsible Investigator; and (b)in part by National Science Foundation grant 8631; Postdoctoral (Postgraduate) Research Associates; H. R. M., J. M. S., C. J. O., (R. E. J.). Antimalarial and phototoxicity test results were supplied by the Walter Reed Army Institute of Research.

*To whom inquiries may be addressed (H. R. M., A. H. Robins Co., Richmond, Virginia 23220).

§Satisfactory spectra were obtained. Instruments: mp, Thomas-Hoover Apparatus; ir, Perkins-Elmer 337, nmr, Hiatachi Perkin-Elmer R-20; mass spectrum, Hitachi Perkin-Elmer RMU 6E. Microanalyses by Gailbraith Lab., Inc. were correct within ±0.4%.

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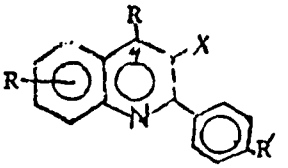
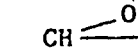
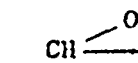
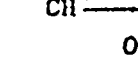
Table II

Quinoline Compounds



Comp No.	Substituents R	R′	X	4-R	Yield[a-o] %	mp° C[p-r]	Analyses[s-w]
1	H	H	Br	$CHOHCH_2NBu_2$	20[b]	147dec	$C_{25}H_{31}BrNO \cdot 2HCl$[t]
2	6,8-Cl_2	Cl	Cl	$CHOHCH_2NBu_2$	96[c]	139.5-141[p,q]	$C_{25}H_{28}Cl_4N_2O$[u]
3	6,8-Cl_2	Cl	F	$CHOHCH_2NBu_2$	87[c]	124-125.5	$C_{25}H_{28}Cl_3FN_2O$[t]
4	6,8-Me_2	Cl	OMe	$CHOHCH_2NBu_2$	59[d]	96-97	$C_{28}H_{37}ClN_2O_2$[t]
12	6,8-Cl_2	Cl	Cl	COOH	65[e]	253dec[p]	$C_{16}H_7Cl_4NO_2$[u]
13	6,8-Cl_2	Cl	F	COOH			$C_{16}H_7Cl_3FNO_2$
14	6,8-Cl_2	H	OMe	COOH	73[f]	217-219dec	$C_{16}H_7Cl_4NO_2$[u]
15	6,8-Cl_2	Cl	OMe	COOH	74[d]	236-237dec[r]	$C_{17}H_{10}Cl_3NO_3$[t]
16	7-Cl	Cl	Cl	COOH	52[e,g]	272dec[p]	$C_{16}H_8Cl_3NO_2$[u]
17	H	H	Br	COCl	49[h]	148-149[p,q]	
18	6,8-Cl_2	Cl	Cl	COCl	86[h]	148-150[p]	$C_{16}H_6Cl_5NO$[u]
19	6,8-Cl_2	Cl	F	COCl	50[i,j]	168-169.5	$C_{16}H_6Cl_4FNO$[t]
20	6,8-Me_2	H	OMe	COCl	89[h]	155-157	$C_{17}H_{10}Cl_3NO_2$[t]
34	6,8-Cl_2	H	OMe	$CONH_2$	-[k]	252-254[p]	$C_{17}H_{12}Cl_2N_2O_2$[t]
32	6,8-Cl_2	Cl	Cl	COOMe	87[i]	207-207.5	$C_{17}H_9Cl_4NO_2$[u]
33	7-Cl	Cl	Cl	COOMe	-	200-201	$C_{17}H_{10}Cl_3NO_2$[u]
29	6,8-Me_2	Cl	OMe	$CH(OMe)_2$	91[f]	154-155[q]	$C_{21}H_{22}ClNO_3$[t]
30	6,8-Me_2	Cl	OMe	CHO	97[f]	136-137[q]	$C_{19}H_{16}ClNO_2$[t]
21	H	H	Br	$COCH_2Br$	60[l]	95-96	$C_{17}H_{11}Br_2CO$[v]
22	6,8-Cl_2	Cl	Cl	$COCH_2Br$	95[g,m,n]	193-193.5	$C_{17}H_8BrCl_4NO$[w]
23	6,8-Cl_2	Cl	F	$COCH_2Br$	64[g,n,o]	178-180	$C_{17}H_8BrCl_3FNO$[t]
25	6,8-Cl_2	Cl	Cl		83[c]	219-219.5	$C_{17}H_9Cl_4NO$[u]
26	6,8-Cl_2	Cl	F		46[g,n,o]	178-179	$C_{17}H_9Cl_3FNO$[t]
31	6,8-Me_2	Cl	OMe		90[f,n]	101-103°[q]	-[q]
5·HCl[4]	6,8-Cl_2	Cl	Me	$CH_2OHCH_2NBu_2$		187-189	$C_{26}H_{32}Cl_4N_2O$[u,x]
8·HCl[4]	6,8-Cl_2	2′,4′-Cl_2	H	"		193-193.5°	$C_{25}H_{21}Cl_5N_2O$[u,x]
9·HCl[4]	6,8-Cl_2	2′,4′-Cl_2	Me	"		178-180°	$C_{26}H_{31}Cl_5N_2O$[u,x]

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Footnotes to Table II

[a]Reasonably pure material unless otherwise specified: recrystallized from: [b]Me_2CHOH-$(Me_2CH)_2O$; [c]AcOEt; [d]Et_2O; [e]EtOH; [f]Et_2O-hexane; [g]Me_2CO; [h]hexane; [i]CH_2Cl_2-hexane; [j]vac sublimed (140°/0.15 mm); [k]$CHCl_3$-hexane; [l]cyclohexanone; [m]petroleum ether (65-100°); [n]partially purified; [o]Me_2CO-CH_2Cl_2; [p]Ir (KBr), cm^{-1}: 2, 2960, 2870, 1460, 1380 (CH_3); 2870, 2830, 1460 (CH_2); 1595, 1540, 1490, 1450 (aromatic). 12, 1710, 1960, 2600, 3430. 16, (from 12, CH_2N_2), 3450, 2525, 1920, 1720. 17, 1760, 18, 1760 (COCl). 22, 1450, 1490, 1540, 1600, 1720, 1390, 2960. 25, 3025, 1240, 905, 828 (epoxide). 32, (from 18, CH_2N_2), 1268 (C-O-C), 1740 (C=O), 2860, 2970 (OMe), 34, (from 20, NH_3), 1760 (C=O), 3180, 3375 (NH_2), 36, 1640 (4-quinolone). Nmr: ($CDCl_3$) δ: 2, 8.89 [d,1,J=2Hz; 5-H], 7.70 [d,2H,J-8Hz,3',5'-H_2], 7.68 [d,1,J=2Hz,7-H], 7.46 [d,2H,J=8Hz, 2',6'-H_2], 5.72 [q,1,J=5Hz,CH), 4.38 (s,1,OH), 2.68 [m,6,(-$CH_2N(CH_2-)_2$], 1.43 (m,4,CH_2CH_2), 0.83 (m,3,CH_3). 22, 7.8 (m,3), 7.5 (m,3), 4.48 (s,2H). 29; 2.51 (s,3,CH_3), 278 (s,3,CH_3), 3.53 (s,3,CH_3), 3.58 (s,6,$2CH_3$), 6.03 (s,1,CHO), 7.28-7.70 (m,3) and 8.05-8.40 (m,3 aromatic). 30; 2.52 (s,3), 2.79 (s,3) and 3.69 (s,3)($3CH_3$), 7.30-7.80 (m,3), 8.05-8.35 (m,2), 8.63 (broad s,1), 10.93 (s,1). 31; 2.53 (s,3, CH_3), 2.80 (s,3,CH_3), 3.07-3.51 (m,2,CH_2) 3.63 (s,3,CH_3), 4.37 (m,1,CH), 7.30-8.30 (m,6,aromatic H). [r]Uv, nm($x10^{-3}$): 15 (prepared like 14), 232 (31.8), 265.5 (32.2), 290-340 (broad plateau, 8.7-9-3). [s]Were within ±0.4% of calcd for C,H, and for: [t]C,H,N; [u]C,H,Cl,N; [v]C,H,Br,N; [w]crude but usable quality; C,H,Br,Cl,N, calcd (found) C, 44.01 (44.78); H, 1.74 (1.74); Br, 17.22 (15.08); Cl, 30.56 (29.60); N, 3.02 (3.21). [x] Syntheses by J. Riedmaier and J. Christensen[4] via Scheme I.

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Antimalarials. 10. Munson, Johnson, Sanders, Ohnmacht, Lutz.

ANALYTICAL DATA

Compound No.	C Found (Calc.)	H Found (Calc.)	N Found (Calc.)	Cl Found (Calc.)	Br Found (Calc.)
1	56.71 (55.93)	6.38 (6.12)	5.54 (5.31)		
2	58.50 (58.38)	5.52 (5.49	5.71 (5.45)	27.39 (27.57)	
3	60.37 (60.31)	5.51 (5.67)	5.57 (5.63)		
4	71.85 (71.70)	8.04 (7.95)	5.76 (5.97)		
5_4	58.50 (58.88)	6.02 (6.09)	5.30 (5.29)	Cl, 6.58 (6.70)	
8_4	55.73 (55.29)	5.48 (5.53)	4.80 (4.96)	Cl, 6.06 (6.28)	
9_4	54.69 (54.51)	5.12 (5.31)	5.28 (5.08)	Cl, 6.43 (6.44)	
12	49.96 (49.65)	1.64 (1.82)	3.46 (3.62)	36.85 (36.64)	
14	58.83 (58.64)	3.08 (3.19)	4.10 (4.03)		
16	54.29 (54.50)	2.10 (2.29)	3.82 (3.97)	30.32 (30.16)	
18	47.65 (47.39)	1.52 (1.49)	3.60 (3.45)	43.75 (43.72)	
19	49.22 (49.40)	1.58 (1.55)	3.55 (3.60)		
20	55.94 (55.70)	2.59 (2.75)	3.92 (3.82)		
21	50.43 (50.40)	2.82 (2.74)	3.41 (3.46)		39.34 (39.45)
22	44.76 (44.01)	1.74 (1.74)	3.21 (3.02)	29.60 (30.56)	15.08 (17.22)
23	45.66 (45.63)	1.87 (1.80)	3.19 (3.13)		
25	52.98 (53.03)	2.31 (2.36)	3.62 (3.64)	36.97 (36.38)	
26	45.66 (45.63)	1.87 (1.80)	3.19 (3.13)		
29	68.01 (67.83)	6.10 (5.96)	3.69 (3.77)		
30	70.00 (70.05)	5.05 (4.95)	4.17 (4.30)		
34	58.87 (58.81	3.30 (3.49)	8.05 (8.07)		
32	50.76 (50.91)	2.03 (2.26)	3.28 (2.49)	35.69 (35.36)	
33	55.65 (55.69)	2.68 (2.75)	3.97 (3.82)	28.70 (29.01)	
36	59.87	3.28	4.90		26.86

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V. Part 6. (Continued)

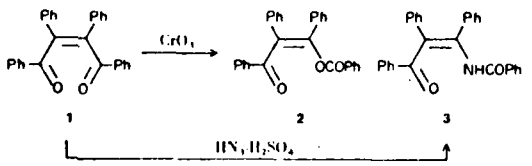
Quinoline Syntheses by Reaction of Hydrazoic Acid with α,β-Disubstituted *cis*-Chalcones (1)

Robert E. Pratt (2ac, 3a, 4ab), William J. Welstead, Jr. (2b, 3b, 4c) and Robert E. Lutz

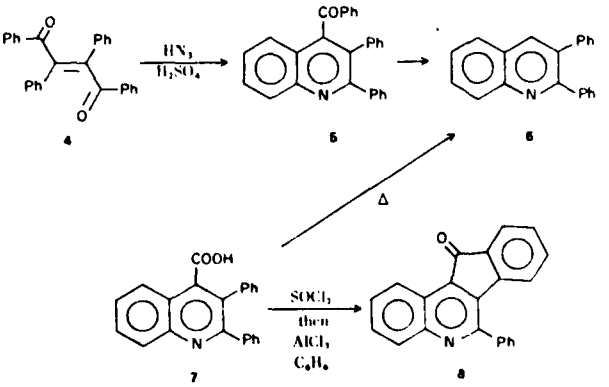
Department of Chemistry, University of Virginia

Hydrazoic-sulfuric acid mixture converted *cis*-α-phenyl-β-benzoylchalcone (*trans*-dibenzoylstilbene, **4**) into 2,3-diphenyl-4-benzoylquinoline (**5**) the structure of which was proved by debenzoylation to 2,3-diphenylquinoline. α,β-Diphenyl and *cis*-α,β-dibromochalcones similarly were converted respectively into 2,3,4-triphenylquinoline (**19**) and 2-phenyl-3,4-dibromoquinoline (**20**). The structure of **19** was shown by difference from the corresponding isoquinoline **21** (synthesized). Smith's mechanism for the analogous conversion of *o*-phenylbenzophenone into 9-phenylphenanthridine through the 9-fluorenol and the 9-hydroazide with loss of nitrogen and ring expansion, was supported by methyl label experiments using 2-(*p*-tolyl)benzophenone which gave a 53:47 mixture of 3- and 8-methyl-6-phenylphenanthridines. Applicability of the mechanism to the reactions with disubstituted *cis*-chalcones was shown by sulfuric acid conversions of two of these into indenol **22** and 2-bromo-3-phenylindenone (**24**), respectively. *trans*-Dibenzoylstilbene underwent resinification in sulfuric acid, giving the quinoline (**5**) only when hydrazoic acid was present.

This investigation stems from the study of 1,2-diaroyl mono and disubstituted ethylenes where *cis*-dicarbonyl group interactions seem to be responsible for certain of their reactions which proceed slowly or not at all with the *trans* isomers (5). For example, *cis*-dibenzoylstilbene (**1**) undergoes ready oxidative rearrangement with carbon-to-oxygen migration of the bulky vinyl moiety, giving the enol-benzoate **2**, whereas under similar conditions the *trans* isomer **4** is inert (4c, 5b). Hydrazoic-sulfuric acid mixture also brings about oxidative rearrangement of **1** but with carbon-to-nitrogen migration of the vinyl moiety, giving the enamine benzoate **3** (5b,6,7).



For comparison, *trans*-dibenzoylstilbene (**4**) was also subjected to the conditions of the Schmidt reaction because, without the proximity of the carbonyl groups, slow reaction or none at all was expected. However, reaction did occur rapidly, giving 2,3-diphenyl-4-benzoylquinoline (**5**), the structure of which was assigned on the basis of its properties and on first but incorrect ideas concerning the mechanism (9a below). This reaction had seemed to take place with retention of the *trans* configuration of **4** by attack of hydrazoic acid at a carbonyl group followed by cyclization involving the sterically adjacent phenyl group, an overall and typically facile *cis*-group interaction.



The structure of quinoline **5** was proved by base-*induced hydrolytic debenzoylation to the known* 2,3-diphenylquinoline (**6**) which was identified by comparison with a sample prepared by decarboxylation of 3-phenylcinchophen (**7**) (8).

Attempts to synthesize quinoline **5** from **7** were unsuccessful because of the excessive steric hindrance at the 4-carbonyl group. The methyl ester and the nitrile of **7** were unreactive toward phenyllithium. Attempted Grignard and Friedel-Crafts condensations of benzene with

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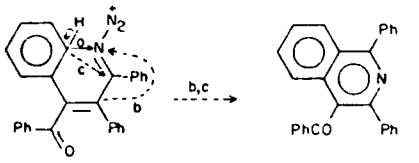
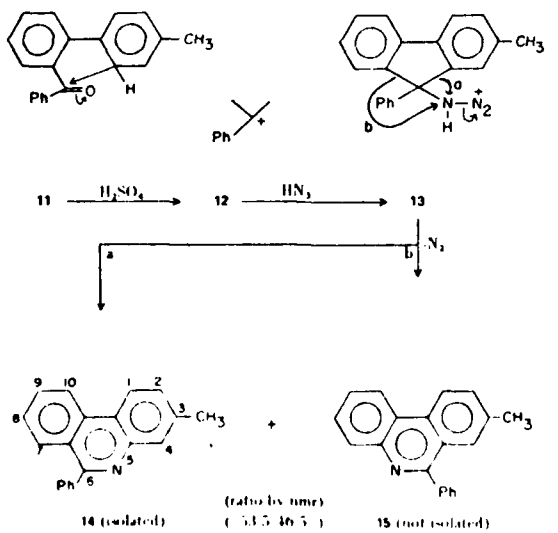
the acid chloride of **7** caused intramolecular dehydrohalogenation to a new compound for which the tetracyclic fluorenone-type structure **8** is suggested on the basis of analysis and ultraviolet and infrared spectra.

Formation of the quinoline **5** by attack of hydrazoic acid at the sterically hindered carbonyl group seemed unlikely although subsequent ring closure **9a** with the proximate phenyl group, would then be possible, facilitated by the buttressing effects of nearby groups. Carbon-to-nitrogen migrations in **9** are excluded because phenyl group migration would have given an anilide, and because migration of the vinyl moiety followed by cyclization **9bc** would have led to isoquinoline **10** rather than to **5**. A mechanism involving hydrazoic acid β-attack on the chalcone system of **4** seemed unlikely, on steric grounds, and because it would not lead directly to quinoline **5**.



9 **10** (not obtained)

In an analogous reaction Smith (9) converted *o*-phenylbenzophenone, *containing the cis-α,β-disubstituted chalcone* system, to 6-phenylphenanthridine, first proposing a mechanism of type **9a** which requires the sterically unlikely initial attack at a carbonyl group, and which is excluded in the cases of the chalcones. He later (6) suggested a preferable mechanism which is without the steric objection and which would account both for his results and ours, namely: cyclodehydration to the 9-fluorenyl cation and the hydroazide, followed by ring expansion by migration of one arm of the fluorenyl system to nitrogen. This mechanism was put to test using the methyl labeled analog, *o*-tolylbenzophenone (**11**).

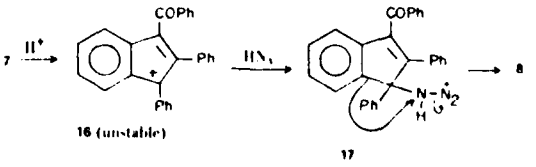


14 (isolated) (53.5 46.5) **15** (not isolated)

The synthesis of **11** was accomplished by a Diels-Alder condensation of butadiene and *trans-p'*-methylchalcone followed by sulfur dehydrogenation, a scheme successfully used in another series (10). The Schmidt reaction converted **11** into a mixture of 3- and 8-methyl-6-phenanthridines (**14** and **15**) from which pure 3-methyl isomer **14** was isolated by fractional crystallization and identified by mixture melting point and infrared comparison with a sample synthesized according to Ritchie (11). The 8-methyl isomer **15** was not isolated from the remaining constant-crystallizing mixture but its presence and concentration were shown by nmr analysis utilizing the 3-methyl peak (δ 2.56) of **14** and the second peak of the mixture at δ 2.46 which was assignable by difference to the 8-methyl group of the isomer **15**. The ratio of the isomers **14**:**15** of 53.5:46.5 was strikingly close to that reported for the hydrazoic acid conversion of 2-methyl-9-fluorenol to the mixture of the 3- and 8-methylphenanthridines (12).

Based on these results, the above Schmidt reaction is best formulated as **11** → **12** → **13** → **14** + **15**. Operation of a mechanism of type **9a** would have led to **15** only; *the first Smith mechanism (of type* **9bc**, *disproved for* **4**) would have led to isomer **14** only; competition between mechanisms seems most unlikely.

Convincing support for the assigned mechanism is the reaction of *o*-benzophenone with hydrogen bromide to give 9-bromo-9-phenylfluorene which is hydrolyzed to the fluorenol (13). In the case of the *trans*-dibenzoylstilbene **4**, concentrated sulfuric acid alone caused resinification; successful conversions to the quinoline **5** required constant presence of excess hydrazoic acid in the reaction mixture. This suggests that the indenyl cation **16** is formed first and is very reactive (it would be destabilized by the β-benzoyl group), but that it is converted through the hydroazide **17** to the quinoline **5**, rapidly, in successful competition with resinification. It is noteworthy that the bulky phenyl arm of the indenyl system of 17 migrates to nitrogen rather than the vinyl arm of the indenyl system or the phenyl group, as would be expected (cf. 6).



16 (unstable) **17**

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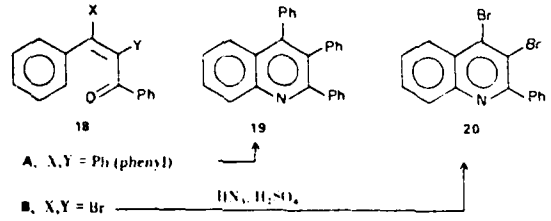
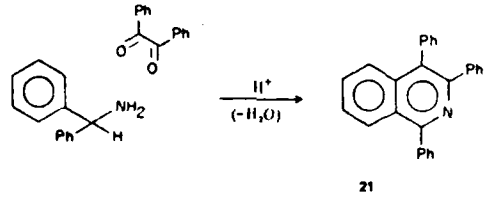
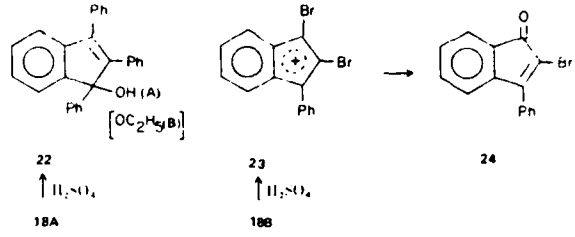
It appears that the essential requirement for a general reaction of the above type is the *cis*-α,β-disubstituted styrylketone system **18** where the *cis* configuration is persistent, where cyclization would be favored, and where an α-group (Y) would induce a hydroazide configuration favorable to migration of the vinyl moiety, with the β-group (X) offering complimentary buttressing effect. As we anticipated, Schmidt reaction conditions did indeed convert α,β-diphenylchalcone (**18A**) (14) into 2,3,4-triphenylquinoline (**19**). *cis*-α,β-Dibromochalcone (**18B**) (15) reacted similarly giving the known 3,4-dibromo-2-phenylquinoline (**20**) (16).



Attempts to prove the structure of 2,3,4-triphenylquinoline (**19**) synthetically by condensation of aniline and phenyldibenzoylmethane, failed. The isomer, 1,3,4-triphenylisoquinoline (**21**), was synthesized by condensing benzhydrylamine and benzil; it proved to be different from quinoline **19**, thereby supporting structure **19** by that difference.



That the mechanism of formation of **19** conformed to the general mechanism outlined above and involved formation of an indenyl cation analogous to, but more stable than, **16**, was shown by treatment of the *cis*-disubstituted ketones (**18A** and **18B**) with concentrated sulfuric acid alone. In the case of **18A**, water and ethanol quenches gave respectively triphenylindenol (**22A**) and its ethoxy analog (**22B**) (17) while the *cis*-dibromochalcone (**18B**) upon water quench gave 2-bromo-3-phenylindenone (**24**) (18).



The new quinoline synthesis promises to be useful although limited in applicability (19).

EXPERIMENTAL (20)

Preparation of β-Phenylchalcone (14,2b).

Pyrolysis of *cis*-1,2-dibenzoylstyrene (350°, 20 minutes, 100 mm.) gave β-phenylchalcone in 45% yield, m.p. 87-89° [lit. 92° (21)]. The Schmidt reaction, giving the anilide (7a), was repeated with identical results.

4-Benzoyl-2,3-diphenylquinoline (**5**).

A 75 ml. chloroform solution of 8 g. of *trans*-dibenzoylstilbene (**4**) (22) and 7 ml. of 1.38 *N* hydrazoic acid in chloroform (0.01 mole) was warmed to 40°. Under vigorous stirring 6 ml. of concentrated sulfuric acid was added dropwise over 30 minutes. Upon cessation of evolution of nitrogen, pouring into ice water, neutralizing with potassium hydroxide, and separation and evaporation of solvent, the residual oil was crystallized from absolute ethanol; 1.6 g. (53%); m.p. 130-132° (not hydrolyzed by hot sodium hydroxide or sulfuric acid); λ *max*: cm^{-1} *1655 (C=O)*; nm. (ε) 237.5 (46,100), shoulders at 252, 262 (41,000, 32,000).

Anal. Calcd. for $C_{28}H_{19}NO$: C, 87.25; H, 4.97; N, 3.63. Found: C, 87.07; H, 5.20; N, 4.12.

It forms an unstable hydrochloride with ether-hydrogen chloride, and a picrate from hot ethanol (m.p. 190-192°).

Action of Concentrated Sulfuric Acid-Chloroform Mixture on **4**.

Within one minute deep red color developed. Quenching in ice gave an oil which neither crystallized nor gave a crystalline product when submitted to the above Schmidt reaction conditions. Tetraphenylfuran failed to react with hydrochloric acid under the above conditions.

Debenzoylation of 4-Benzoyl-2,3-diphenylquinoline (**5**) to 2,3-Diphenylquinoline (**6**).

An intimate mixture of 2 g. of **5**, 5 g. of powdered potassium hydroxide and 1 ml. of water was heated until the water and an oil had distilled. The oil (**6**) was extracted by ether, washed with acid and then base, isolated by evaporation of solvent, and added to 20 ml. of saturated ethanolic picric acid (heated). The **6**-picrate separated and was recrystallized from ethanol [yellow, 1.4 g. (44%)]; m.p. 224-225°. Its ir spectrum was identical to that of a sample of m.p. 223-225° (*20a*) prepared from authentic 2,3-diphenylquinoline [m.p. 88-89°; made by decarboxylation of **7** (8)].

Anal. Calcd. for $C_{27}H_{18}N_4O_7$: C, 63.53; H, 3.55. Found: C, 63.47; H, 3.59.

3-Phenylcinchophen (**7**) (8) and its Methyl Ester, Amide and Nitrile.

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The acid **7** was prepared according to Pfitzinger (8) by condensation of isatin with desoxybenzoin (33% ethanolic potassium hydroxide) (20a); λ max: cm^{-1} 1755 (C=O); nm. (ε) 236, 330 (40,000, 8,270).

The methyl ester of **7** was made from the acid chloride of **7** by methanolic sodium methoxide (reflux, 1 hour); recrystallized from methanol; 51%, m.p. 138-139°; λ max: cm^{-1} 1715 (C=O); nm. (ε) 237, 258, 332 (36,100, 25,700, 7,000). It did not react with phenyllithium in ether (toluene, reflux 3 hours).

Anal. Calcd. for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.70; H, 5.02; N, 4.58.

The amide of **7** was prepared in a new way (95%) from 7-acid chloride and concentrated ammonium hydroxide; m.p. 276-278° (23a); ν 1670 cm^{-1} (C=O), 3170, 3310 (NH).

The nitrile (of **7** (23b)) was prepared in a new way from the 7-amide by phosphorus pentoxide in tetrachloroethane (reflux 2 hours); m.p. 154-155°; ν 2220 cm^{-1} (C≡N); λ (ethanol) 246, 345 nm, ϵ^{-3} 31.3, 6.95; no reaction with phenylmagnesium bromide (ether, reflux 12 hours) or with phenyllithium (toluene, reflux 3 hours.).

3-Phenylcinchophen Acid Chloride.

A solution of 10 g. of **7** in 40 ml. of thionyl chloride was refluxed for 12 hours and evaporated. Benzene extraction of the residual oil, evaporation under reduced pressure and crystallizations of the residue from petroleum hexane-benzene mixture and from isooctane gave 7 g. of the acid chloride (60%); m.p. 140-142°; λ max: cm^{-1} 1780 (C=O).

Anal. Calcd. for $C_{22}H_{14}ClNO$: C, 76.85; H, 4.10. Found: C, 76.47; H, 3.91.

6-Phenyl-11-oxo-11*H*-indeno[1,2-*c*]quinoline (**8**).

To a mixture of 20 ml. of dry benzene and 0.8 g. of aluminum chloride was added dropwise a 10 ml. benzene solution of **7**-acid chloride. After stirring for one hour, hydrolysis of the red solution with ice-hydrochloric acid and crystallizations from absolute ethanol-benzene mixture and from glacial acetic acid gave orange crystals; 0.55 g. (62%), m.p. 259-261°; λ max: cm^{-1} 1730 (C=O); nm. (ε) 265 (47,000).

It was also obtained (8%) upon reaction of the acid chloride for 45 minutes with refluxing ethereal phenylmagnesium bromide (recovery of acid chloride 17%).

Anal. Calcd. for $C_{22}H_{13}NO$: C, 85.97; H, 4.26. Found: C, 85.71; H, 4.17.

Preparation of α,β-Diphenylchalcone (**18A**) (14,2b).

Pyrolysis of *cis*-dibenzoylstilbene (**1**) at 320° (20 minutes) and recrystallization from glacial acetic acid, gave **18A** in 78% yield, m.p. 152-153°; λ max: cm^{-1} 1660 (C=O).

Action of Concentrated Sulfuric Acid on α,β-Diphenylchalcone (**18A**).

While stirring, 5 ml. of concentrated sulfuric acid was added over 2 minutes to a solution of 12% of **18A** in 50 ml. of dry chloroform. The red solution after 5 minutes was quenched with ice. Evaporation of the washed and dried chloroform extracts and crystallization of the residual oil from hexane (requiring 2 days), gave 1,2,3-triphenylinden-1-ol (**22A**), m.p. 128.5-130.5° (20a) [lit. 129° (17)]. Another run with quenching in absolute ethanol gave 1-ethoxy-1,2,3-triphenylindene (**22B**); m.p. 172-173.5° (20a) [lit. 172° (17)].

2,3,4-Triphenylquinoline (**19**).

To a 75 ml. chloroform solution of 5 g. (0.12 mmoles) of **18A** and 18 ml. (15 mmoles) of 0.87 *N* hydrazoic acid in chloroform, was added dropwise with stirring (5°) 10 ml. of concentrated sulfuric acid (over 0.5 hours). After warming to room temperature, quenching in ice, and neutralization with aqueous sodium hydroxide, the chloroform solution was dried over sodium sulfate and evaporated. Recrystallization from absolute ethanol gave 1.75 g. (35%); m.p. 189-190°; λ max: nm (ε) 247, 298, 335 (47,600, 14,660, 12,480).

Anal. Calcd. for $C_{27}H_{19}N$: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.68; H, 5.23; N, 4.38.

1,3,4-Triphenylisoquinoline (**21**).

A mixture of 5 g. of benzhydrylamine and 5.5 g. of benzoin was melted at 150° (10 minutes). Addition of 20 ml. of mineral oil, heating at 280° (20 minutes), cooling, and addition of 10 ml. of ether gave a solid which was crystallized from hexane; m.p. 208-209°.

Anal. Calcd. for $C_{27}H_{19}N$: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.58; H, 5.89; N, 3.76.

Schmidt Reaction on *cis*-α,β-Dibromochalcone (**18B**).

To 10 ml. of chloroform, 0.5 g. (1.4 mmoles) of **18B** (15) and 1.5 ml. of 1.03 *N* hydrazoic acid in chloroform, was added dropwise with stirring, 1.5 ml. of concentrated sulfuric acid. After 2 hours, quenching in ice, neutralization, separation, and evaporation of the chloroform, gave a residue of 2-phenyl-3,4-dibromoquinoline (**20**) (0.2 g.) which was recrystallized from ethanol; 0.15 g. (30%), m.p. 148-149° (20a); identified by ir comparison with an authentic sample (16c).

Action of Concentrated Sulfuric Acid on *cis*-α,β-Dibromochalcone (**18B**).

A mixture of 4 g. of **18B** and 10 ml. of concentrated sulfuric acid in 100 ml. of chloroform at 40° was stirred for 10 minutes, quenched in ice, and neutralized. Evaporation of combined and dried chloroform extracts gave an oil which was placed on an alumina column by dry benzene and eluted with hexane-benzene mixtures; this gave small amounts of *cis* and *trans* **18B**, and then 1.5 g. of the yellow-orange 2-bromo-3-phenylinden-1-one (**24**), m.p. 111-113° [lit. 112-113° (18)]. This was identified by analysis (20a), mixture melting point and ir comparison with a sample synthesized from β,β-diphenylpropionic acid [m.p. 149-153° (18b,c)] through dehydration to 3-phenylindan-1-one [m.p. 73-76° (18d)], bromination to the dibromide [m.p. 120-123° (18a)], and pyridine dehydrobromination to **24** [m.p. 111-113° (18a)].

Synthesis of 3-Methyl-6-phenylphenanthridine **14** (11).

2-Nitro-4-methyldiphenyl (b.p.$_{1.6}$ 140-142°) (11) was reduced by treatment of a stirred mixture of 27 g. (0.127 mole), 250 ml. of 95% ethanol and palladium on charcoal (50°), with 15 ml. of hydrazine hydrate added dropwise over 30 minutes. Another 0.1 g. of catalyst was added with refluxing (1 hour). Filtration, washing with ethanol, and concentration to 50 ml. and addition of 50 ml. of hot water, gave an oil which was distilled; 23 g. (98%), b.p.$_{1.5}$ 126-128° (cf. 11). Treatment of 20 g. (0.109 mole) of the oil in 15 ml. of pyridine and 23 g. of benzoyl chloride (100°, 20 hours), followed by 75 ml. of 5% sodium bicarbonate and extraction with 100 ml. of benzene and evaporation, gave 2-benzamido-4-methyldiphenyl; 21 g. (67%), m.p. 90-92° (cf. 11). Cyclization of 2 g. (7 moles) by 4 ml. of phosphoryl chloride (reflux, 8 hours), evaporation under reduced pressure, extraction with 25 ml. of benzene, evaporation, and crystallizations from

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benzene gave 1.8 g. (96%) of **15**: m.p. 116-118° [analyzed (20a)] [picrate, m.p. 238-245° dec. (11)]. Nmr (carbon tetrachloride), δ 8.0 (m, 12H, aromatic) 2.56 (s, 3H, CH_3).

4-Benzoyl-5(4-tolyl)-cyclohexene.

A mixture of 111 g. (0.5 mole) of 4-methylchalcone [m.p. 94-96° (cf. 24)], 120 ml. of absolute ethanol and 54 g. (0.5 mole) of butadiene, was heated in a steel reactor for 12 hours at 170°. Cooling gave 60 g. (37%); the product after recrystallization from *n*-hexane and ethanol had m.p. 83.5-85°; λ max: cm^{-1} 1678 (C=O).

Anal. Calcd. for $C_{20}H_{20}O$: C, 87.00; H, 7.24. Found: C, 86.94; H, 7.51.

2(*p*-Tolyl)benzophenone (**11**).

A mixture of 27.6 g. (0.1 mole) of 4-benzoyl-5-(*p*-tolyl)-cyclohexene and 6.4 g. (0.2 mole) of sulfur was heated for 1 hour at 200-230° and then for 2 hours at 260°. Distillation under reduced pressure and crystallization from hexane gave 4.1 g. (15%) of **11**, m.p. 77-79°; λ max: cm^{-1} 1671 (C=O).

Anal. Calcd. for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.41; H, 5.97.

The Schmidt Reaction on **11**.

This was carried out on 8 g. (0.0294 mole) in 80 ml. of stirred concentrated sulfuric acid at 50° by portionwise addition of 3 g. (0.046 mole) of sodium azide over 3 hours, stirring for an additional 12 hours, quenching in ice, filtration of the precipitate, solution of the precipitate in 200 ml. of ether, extraction with 50 ml. portions of 10% hydrochloric acid, and neutralization with 10% sodium hydroxide. The resulting orange oil (3 g.) was taken up in hexane, placed on a 60 g. florisil column, and eluted with 8:92 ether-benzene mixture which gave 2.8 g. of **14-15** mixture, m.p. 100-113°. Fractional crystallizations from hexane gave 9.0 g. of pure **14**, m.p. 116-118°; identified by correct analysis (20a), spectral comparison, and mixture m.p. with authentic **14** synthesized as above (11). The 1.9 g. of material from the combined filtrates from **14** was not resolved by further crystallizations and was a constant melting mixture, m.p. 97-106°; it showed gradual rise in melting point when mixed with increments of pure **14**, and gave correct C, H analysis for $C_{20}H_{15}N$. Its nmr spectrum showed a 12 proton aromatic multiplet resembling that of **15**, and two methyl singlets, one of δ 2.56 (**14**), and the other δ 2.46 which represents the one possible structural isomer, namely, 8-methyl-6-phenylphenanthrene (**15**) (not isolated pure). From the yield of pure **14** isolated, and the amounts of the two isomers in the mixtures obtained (estimated from the intensities of the respective nmr methyl peaks) the ratio of the isomers **14**:**15** was 53.5:46.5.

Acknowledgment.

Repetitions of the Schmidt reaction on **18B** and identification of **20** were carried out by Richard E. Johnson (16c,19).

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(3) Present locations: (a) Union Oil Co., Research Center, Brea, California. (b) A. H. Robins Co., Richmond, Virginia.

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(20) Melting points are corrected. Instruments: Infrared: Perkin-Elmer 137 or 337, potassium bromide pellet. Ultraviolet: Perkin-Elmer 4000-A or Beckman DK-2, 5×10^{-5} *M* (ethanol). NMR: Varian A-60, deuteriochloroform (tetramethylsilane). (a) Known compound: analyzed correctly for C, H ± 0.4%.

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V. Part 7. A 2-Vinylog of 2-Aryl-4-quinoline Aminoalcohols, Based on the 2,3-Trimethylene-quinoline Nucleus.

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Antimalarials. 8[1].

2,3-Trimethylene-4-quinoline Amino Alcohols. 5,7-Dichloro-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-(α-di-*n*-butylaminomethyl)methanol

J. M. Sanders,[2] D. P. Clifford,[2] and R. E. Lutz*

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

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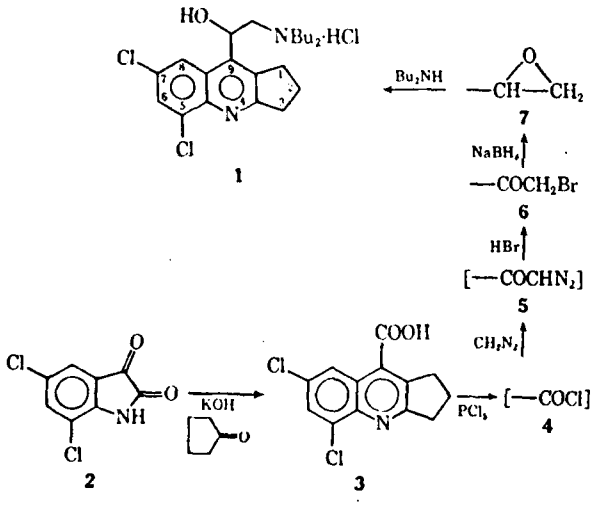
The title compound (**1**) was synthesized to provide, for antimalarial testing, an example of a 4-quinoline amino alcohol in which position 2 was blocked by the CH_2 group of the rigid 2,3-trimethylene ring.[3] It was hoped that this arrangement would prevent rapid bio-



degradation,[4] and, through lack of conjugation of the type involved in the 2-aryl series, would minimize phototoxicity.[5]

The synthesis started from 5,7-dichloroisatin (**2**) and proceeded by the classical route,[6] namely, Pfitzinger condensation with cyclopentanone to 6,8-dichloro-2,3-trimethylenecinchoninic acid (**3**),[7] followed by diazomethylation of the acid chloride **4** to **5**, hydrobromination to bromo ketone **6**, reduction by $NaBH_4$–NaOH to the epoxide **7**, and aminolysis with Bu_2NH.

Biological Activity.[1d,8] Target compound **1** proved to be only moderately active against *Plasmodium berghei* in mice, doubling survival time at a dosage of 320 mg/kg and trebling it at 640 mg/kg.

Experimental Section[9]

6,8-Dichloro-2,3-trimethylenecinchoninic Acid (5,7-Dichloro-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-carboxylic Acid) (3) (*Cf.* **the Unchlorinated Acid**[7]).—The purple slurry from addition of 21.6 g (0.1 mole) of **2** to 16.8 g (0.3 mole) of KOH in 125 ml of H_2O was added under stirring to 20 g (0.238 mole) of cyclopentanone in 150 ml of abs EtOH. After refluxing (25 hr) and evapn *in vacuo*, the residue was dissolved in 700 ml of H_2O. Acidification with AcOH gave **3**; this was dissolved in KOH–H_2O, repptd by AcOH, and washed successively with dil AcOH, H_2O, and cold EtOH: 23 g (81.6%); mp 272–274° dec. *Anal.* ($C_{13}H_9Cl_2NO_2$) C, H, N.[9b]

3-Potassium Salt (8).—A hot soln of 5 g of KOH in 20 ml of abs EtOH was added with stirring to a suspension of 21.9 g of **3** in 150 ml of warm EtOH. Chilling, filtering, and washing with cold EtOH and with 250 ml of Et_2O gave 21.47 g: unchanged at 325°; ir (cm^{-1}) 2975, 2930, 1580 (C=O). *Anal.* ($C_{13}H_8Cl_2KNO_2$) C, H, N.

3-Methyl ester (9) was prepd by CH_2N_2–Et_2O on **3**; crystd from EtOH–hexane: mp 177–178°; ir (cm^{-1}) 1720 (C=O); nmr ($CDCl_3$), δ 8.30 (1 H, doublet), 7.30 (1 H, d), 4.13 (3 H, *s*), 3.31 (4 H, triplet), 2.25 (2 H, quintuplet). *Anal.* ($C_{14}H_{11}Cl_2NO_2$) C, H, N.

3-Amide (10) was prepd from **4** by aq NH_3; crystd from Et_2O–hexane: mp 285–287° dec; ir (cm^{-1}) 3350, 3160, 1680. *Anal.* ($C_{13}H_{10}Cl_2N_2O$) C, H, N.

6,8-Dichloro-4-bromoacetyl-2,3-trimethylenequinoline (6).—A C_6H_6 soln of **3-acid chloride, 4**,[10] was prepared from 13.8 g of 3-HCl by reaction with PCl_5 (100°, 30 min) and extg with dry C_6H_6[11] (quenching of an aliquot in ice–NH_3 gave **10**). This was added (below 10°, over 0.5 hr) to 5.61 g of dry CH_2N_2 in 700 ml of Et_2O (KBr pellets; H_2O present at this point readily converts **4** through **3** and CH_2N_2 to **9**). After warming to room temp (2 hr) 48% HBr–H_2O was added (stirring, 40 min). The Et_2O layer was washed successively with 48% HBr, H_2O, and NaCl–H_2O, dried ($MgSO_4$), and evapd *in vacuo*. The residual oil in 700 ml of petr ether (bp 65–110°) was decolorized (charcoal, reflux) and successively coned and cooled giving **6**: recrystd (hexane), mp 125–127° (still impure); ir (cm^{-1}) 3090, 3000, 2970, 2940, 1720; nmr ($CDCl_3$), 7.80 (1 H, d), 7.60 (1 H, d), 4.38 (2 H, s), 3.21 (4 H, overlapping triplets), 2.37 (2 H, quintuplet).

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(8) The method of T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(9) Instruments: (a) Thomas-Hoover apparatus for mp; (b) ir, Perkin-Elmer 337; (c) nmr, Varian Perkin Elmer R-20; (d) anal. (Gailbraith Lab, Inc.) were correct within ±0.4%.

(10) First attempted prepns of **4** using PCl_5 were frustrated by facility of hydrolysis. Use of $SOCl_2$ (with or without DMF), and oxalyl chloride [J. Szmuszkovic, *J. Org. Chem.*, **29**, 843 (1964)], gave amorphous orange products, except in one of the latter experiments using 3-K salt (**8**) (not successfully repeated) which MeOH quench gave 3-Me ester (**9**, 87%).

(11) Cf. the tetrahydroacridine analogs: G. K. Patnaik, M. M. Vohra, J. S. Bindra, C. P. Garg, and N. Anand, *J. Med. Chem.*, **9**, 483 (1966).

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6,8-Dichloro-4-epoxyethyl-2,3-trimethylenequinoline (7).—A soln of 1 g (0.026 mole) of $NaBH_4$ in 10 ml of H_2O and 7 ml of 2 *N* NaOH, was added dropwise over 10 min to a stirred suspension of 4.65 g (0.013 mole) of nearly pure **6** (above) in 50 ml of MeOH. Stirring for an addl 1.5 hr, cooling for 15 min, filtering, and washing with MeOH gave 3.42 g (94.5%) of **7** (mp 134–139°); recrystd from Et_2O–hexane, mp 144–145°; ir (cm^{-1}) 2960, 2980, 3100, none for C=O; nmr ($CDCl_3$), 8.02 (1 H, d), 7.71 (1 H, d), 4.26 (1 H, m), 3.10 (5 H, m), 2.17 (2 H, quintuplet). *Anal.* ($C_{14}H_{11}Cl_2NO$) C, H, N.

5,7-Dichloro-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-(α-di-*n*-butylaminomethyl)methanol·HCl (1).—A suspension of 3.6 g of **7** in 12 ml of Bu_2NH was stirred for 4.5 hr at 105–110°, monitoring disappearance of **7** (4 hr) by tlc (silica gel G, 1:1 Et_2O–hexane). After evapn *in vacuo* of Bu_2NH (60°) the oil (5.1 g), dissolved in 150 ml of Et_2O, was treated with increments of Et_2O·HCl, each sufficient to give 0.2–0.4 g of **1** (each fraction being washed with Et_2O). Fractions 1–4 contd decreasing amts of Bu_2NH·HCl; and 5–8 were largely **1** (2.65 g). Repeated recrystn from EtOH–Et_2O gave 0.5 g, light tan, mp 160–162° dec; ir (cm^{-1}) 3440, 3220 (OH), 2960, 2940, 2880 (CH), 2670, 2620, 2530 (NH). *Anal.* ($C_{22}H_{30}Cl_2N_2O$·HCl) C, H, N, Cl.

Incidental and Preliminary Experiments. Attempts to add 2-PyLi and MeLi to the 2,3-trimethylenecinchoninic acids were unsuccessful, presumably because of steric interference of the 3-CH_2 group and/or the activity of the 2-CH_2 hydrogens (*cf.* ref 12).

2,3-Trimethylenecinchoninic acid·HCl (11), pptd from Et_2O, mp 252–255° dec, was treated with PCl_5 (steam bath for 30 min, addn of C_6H_6, and reflux for 2 hr), giving a ppt presumed to be the **acid chloride·HCl (12)** (sublimed, 8%, mp 245° dec).

2,3-Trimethylenecinchoninamide (13) was prepd from **12** by treatment with H_2O–NH_3; crystd from EtOH, mp 276–277°; ir (cm^{-1}) 3330 (s), 3140 (s) (NH_2), 1688 (C=O). *Anal.* ($C_{13}H_{14}N_2O$) C, H.

4-Bromoacetyl-2,3-trimethylenequinoline·HBr (14).—CH_2N_2–Et_2O with 3 g of **12** (overnight) gave orange cubes of diazo ketone. Treatment with 10 ml of 48% HBr–H_2O gave **14**; crystd from EtOH; 2.1 g (70%); mp 208° dec; ir (cm^{-1}) 1730 (C=O), 2500 (NH). *Anal.* ($C_{14}H_{13}Br_2NO$) N.

Derivatives of 2,3-trimethylene-4-quinolones were made by the action of the appropriate aniline on ethyl cyclopentanone-2-carboxylate, cyclizing at 250°, and crystn from EtOH:[3b,13] **15,** (*a*) 6,8-Cl_2, 26%, mp 305–307° (*b*) cyclization by refluxing Ph_2O, recrystd, mp 314–315° (lit.[3b] 313°) [*Anal.* ($C_{12}H_9Cl_2NO$) C, H, N]; **16,** 6,8-Me_2, 60%, mp 326–327° [*Anal.* ($C_{14}H_{15}NO$) N]; **17,** 6-Me, 39%, mp 319–322° [*Anal.* ($C_{13}H_{13}NO$) C, H]; **18,** 8-OMe, 26%, mp 212–213° [*Anal.* ($C_{13}H_{13}NO_2$) C, H, N]; **19,** 8-Cl, 21%, mp 269–270° [*Anal.* ($C_{12}H_{10}ClNO$) C, H, N]; **20,** 8-F, 15%, mp 292–293° [*Anal.* ($C_{12}H_{10}FNO$) C, H, N].

4-Bromo-2,3-trimethylenequinolines were prepd by treating the quinolone[13] with $POBr_3$ at 120°; crystd from EtOH: **21** (parent compd), 50%, mp 72–73° [*Anal.* ($C_{12}H_{10}BrN$), C, H, N]; **22,** 6,8-Me_2, from **16,** 69%, mp 124–125° [*Anal.* ($C_{14}H_{14}BrN$) C, H].

4,6,8-Trichloro-2,3-trimethylenequinoline (23) was prepd by refluxing $POCl_3$ on **15,** crystd from EtOH, 80%, mp 160–162°. *Anal.* ($C_{12}H_8Cl_3N$) C, H, N.

Attempted preparation of 4-lithio-2,3-trimethylenequinolines from **21** and **22** by BuLi and addns to 2-pyridaldehyde were unsuccessful, presumably because of the activities of the 2-CH_2 groups.[12]

(12) P. G. Campbell and P. C. Teague, *J. Amer. Chem. Soc.*, **76,** 1371 (1954).

(13) D. K. Blount, W. H. Perkin, Jr., and S. G. P. Plant, *J. Chem. Soc.*, 1975 (1929).

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V. Part 7. (Continued)

Antimalarials. 11[#] Vinylogs of Substituted 2-Aryl-4-quinoline Aminoalcohols. 3-(p-Chlorobenzylidine)-5,7-dimethyl-1,2-dihydro-1H-cyclopenta[b]quinoline-9 and 2-p-Chlorostyryl-6,8-dimethyl-4-quinoline (α-Di-n-butylaminomethyl)methanols.

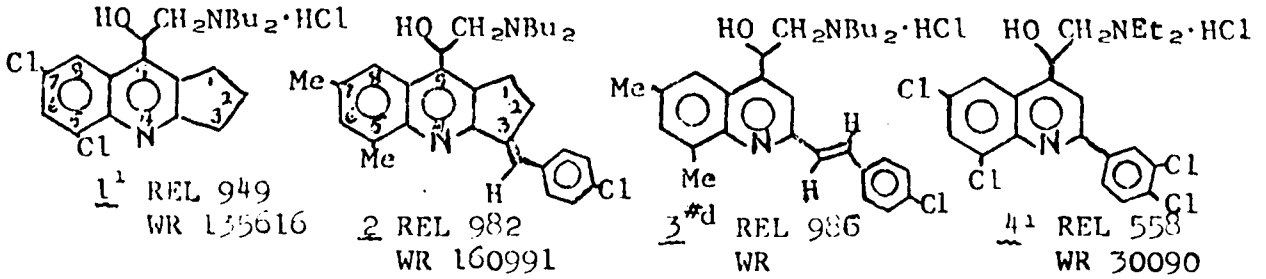
Manuscript. To be submitted to the Journal of Medicinal Chemistry.

By J. M. Sanders[§] and R. E. Lutz* (Supplements: by B. B. Corson, J. Pociask, H. Koppel and J. Riedmaier,[§] and by R. G. Bass and R. R. Hirjibehdin[11]).

Department of Chemistry, University of Virginia, Charlottesville, Va.

Abstract. Syntheses were from 6,8-dimethyl-4-hydroxycarbostyril by 3,3-dichlorination, dimethoxylation to the 3-ketal, hydrolysis to the glyoxal acetal, Pfitzinger condensation with cyclopentanone or acetone to the 2,3-trimethylene or 2-methylquinoline, condensation with 4-ClPhCHO at the 2-methylene or methyl group, hydrolysis to the 4-quinaldehyde, methylenation to the epoxide, and condensation with Bu_2NH. The first was curative against P. berghei in mice at 40 mg/kg.

Since 6,8-dichloro-2,3-trimethylene-4-quinoline-(α-di-n-butylaminomethyl)methanol (1)[1] was moderately active against P. berghei in mice and non-photoxic in animals, the p-chlorobenzylidine 6,8-dimethyl analog 2 and the parent 2-p-chlorostyryl-4-quinoline aminoalcohol 3 were synthesized for comparisons with the highly curative 2-aryl-4-quinolyl aminoalcohols of type 4[2]. Compound 2 has a rigid tricyclic nucleus in which the quinoline moiety is conjugated through the 2-vinyl group with the p-ClPh in a presumably-trans and relatively planar chalcone-like system where the 1,2-quinoline C=N replaces the chalcone C=O; and 3 has the simple trans-chalcone-like system planarized by resonance.



1[1] REL 949 WR 135616

2 REL 982 WR 160991

3[#d] REL 986 WR

4[1] REL 558 WR 30090

Chemistry. In an attempted synthesis of the 5,7,4'-trichloro analog of 2, p-ClPhCHO was condensed at the active CH_2 of the 2,3-trimethylene carboxylic ester (39→40), but the acid chloride on diazomethylation and hydrobromination[2a] failed to give the bromoketone and exhausted supplies of intermediates. The Ziegler synthesis[3] of 4-quinaldehydes was then utilized, starting from $2,4\text{-Me}_2\text{PhNH}_2$ rather than the preferred $2,4\text{-Cl}_2\text{PhNH}_2$ because of the reported much better yield of intermediate 9 (Scheme I). Condensation of ethyl malonate

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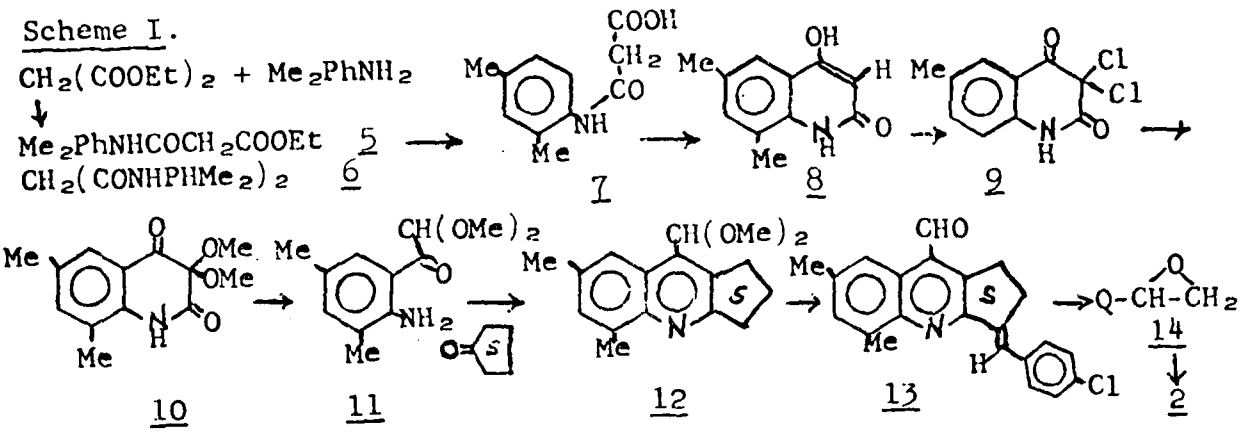
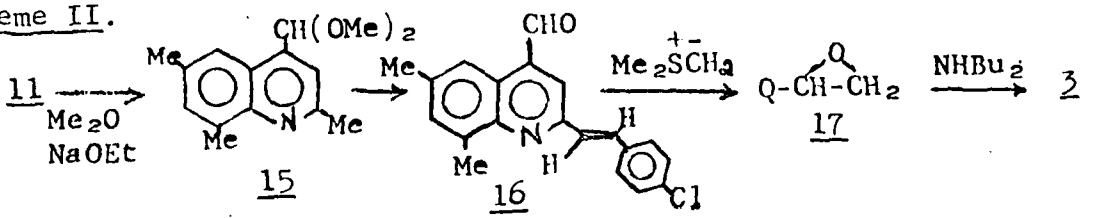
with 2,4-Me_2PhNH_2 and hydrolysis of 5 gave malonamic acid 7. Cyclization to 6,8-dimethyl-4-hydroxycarbostyryl (8), 3,3-dichlorination to 9, dimethoxylation to the 3-ketal 10, and hydrolysis, gave glyoxal acetal 11. Pfitzinger condensation with cyclopentanone to the 2,3-trimethylenequinoline 12, condensation at the 2-CH_2 with 4-ClPhCHO, hydrolysis to quinaldehyde 13, methylenation[4] to the epoxide 14, and condensation with Bu_2NH, gave aminoalcohol 2.

Scheme I.



The route to the parent 2-vinylog of the 2-aryl-4-quinoline aminoalcohols, 2-(4-chlorostyryl) analog 3, branched from Scheme I by condensation of 11 with acetone.

Scheme II.



Antimalarial Activity.[5] The 2-p-chlorobenzildine-2,3-trimethylene-4-quinoline aminoalcohol 2 was active against P. berghei in mice at 10 mg/kg, cured 2 of 5 mice at 20 mg/kg, and was completely curative at 40 mg/kg. It was mildly phototoxic in animals (MED, ip, mg/kg: 100).

Considering the manifold increases in antimalarial activity in other series upon replacing 6,8-Me_2 by more effective pharmacophoric groups,[6] it would be of interest to make and test the 6,8-Cl_2 and CF_3 analogs of 2, and representative cis isomers[cf 2d] and saturated analogs.

Syntheses of 2,3-Trimethylene Compound 2 and its α-Piperidyl Analog by classical routes [2a,7] were undertaken by Corson, Riedmaier, Pociask and Koppel[8] to obtain a sample for clinical trial. The last step condensation of aminoalcohol 24[8] with p-ClPhCHO (Scheme III) gave only 3% of 2, possibly because of sensitivity of the aminoalcohol chain with its active 4-methine group.

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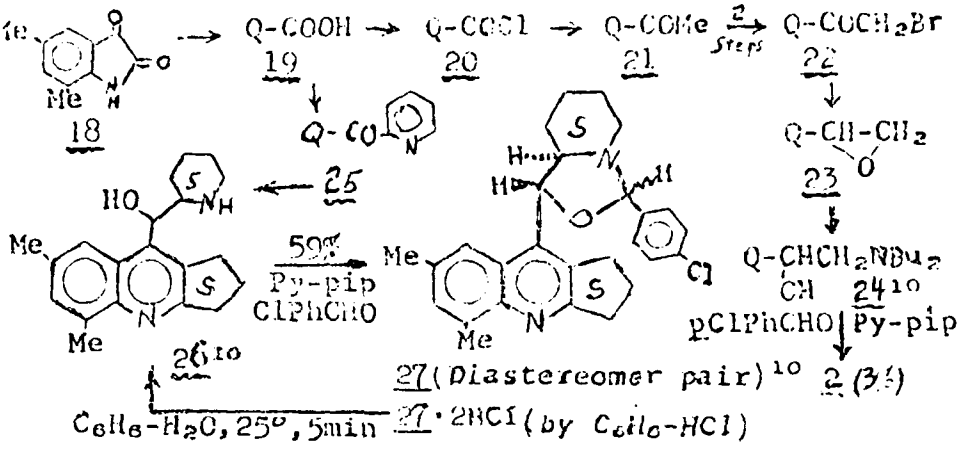
Scheme III.

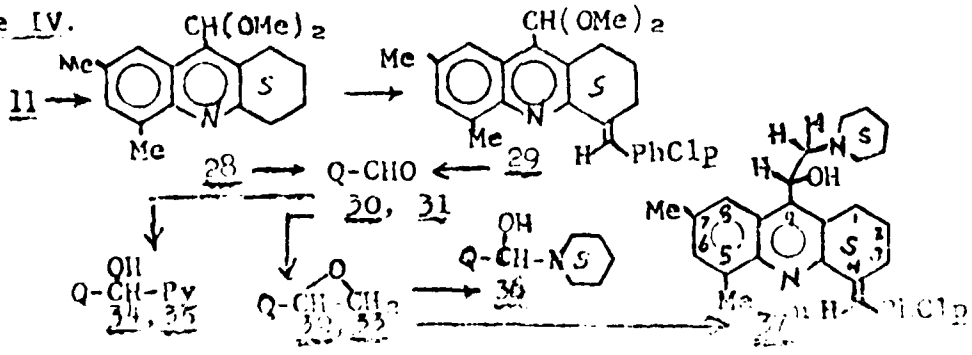


Attempted synthesis of the 2-piperidyl analog of 2, via pyridylation of 19 to 25,[cf.7] hydrogenation to 26, and condensation with p-ClPhCHO, gave, instead of the desired aminoalcohol, an isomer which has now been shown to be the oxazolidine 27, the cyclic azaketal of the secondary amino alcohol 26.[cf8,9] Possibly the azaketal group might serve protectively in forced condensations at the 2-methylene group, to be followed by the very facile acid-hydrolytic regeneration of the secondary aminoalcohol group.[3c]

Proof of structure 27 rests on: (a) Total inactivity against P. berghei in mice in contrast to total curativity of 2 at 40 mg/kg[#,5]. (b) Facility at 25° of hydrolytic cleavage[8,9] of 27·2HCl to 26 and p-ClPhCHO[8]. (c) Absence of N-H and O-H ir absorptivity at 3,400-3,500 cm^{-1} (KBr or $CHCl_3$)(shown by 2). (d) Lack of chalcone type uv absorptivity above nm 350 (shown by 2). (e) Nmr spectra compatability with 27 as a pair of diastereomers[10] (unseen by tlc): δ, $CDCl_3$(or C_6D_6), 5.70, 6.16, J8, Hz 26(30), IH-dd with all-equal peak intensities rather than the 1:2 peak-intensity ratios calculated for each of the doublets were they coupled (LACOON III, least squares fit simulation). D_2O caused no D exchange required by O-H and D-H. (f) Chemical ionization mass spectrum (D. F. Hunt[10]): substituting D_2O for H_2O as reagent gas failed to increase the molecular weight of the abundant M+1 ion (M+H m/e 433, M+D m/e 434), thus excluding O-H and N-H (spectrum compatible).

Syntheses of 5,7-Dimethyl-4-(p-chlorobenzilidine-1,2,3,4-tetrahydroacridine-9-(α-N-piperidinomethanol)methanol(37), a 2,3-tetramethylenequinoline analog of 2, by Bass and Hirjibehdin[11], was accomplished via Scheme IV in spite of evident steric interference with reactions of groups at position-9 (paralleling Scheme I) (an antimalarial test sample has not yet been obtained).

Scheme IV.



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Experimental.[†]

Synthesis of 2 started with reaction of 2,4-dimethylaniline and diethyl malonate (1:6 mixture, 190° until evolution of EtOH ceased).[cfa] Mixtures of 5 and 6 were obtained by pouring into MeOH (chilling), concentrating in vaco (recovering diethyl malonate), and extraction of the residue (boiling Et_2O). Recrystallization (Et_2O-hexene) gave ethyl N-(2,4-dimethyl phenyl)malonamate (5); mp 102-104°; characterized by ir (cm^{-1}), 3340, 3320, 1730, 1675; anal. by nmr ($CDCl_3$): δ1.21 (t,3, J = 7.5 Hz), 2.30 (s,6), 3.49 (s,2), 4.28 (q,2, J = 7.5 Hz), 7.08 (m,2), 7.81 (s,1), 9.15 (s, broad, 1). Two successive treatments of 5-6 mixture with boiling 10% $NaHCO_3$ (6 hr), cooling and filtration, gave malonic acid bis-2,4-dimethylanilide (6); mp 126-164° (containing no 5, tlc, silica gel G, EtOH); characterized by mass spectrum, m/e 310 (M^+), 163, 149, 148, 122, 121 (base peak), 120, 106, 77 (this should be convertible to 10 by $AlCl_3$).[3c] Acidification of $NaHCO_3$ filtrates from 6 (HCl) precipitated N-(2,4-dimethylphenyl)malonamic acid (7); recrystallized (EtOH) (75%), mp 158-159°; mass spectrum, m/e 207 (M^+), 163, 122, 121 (base peak), 120, 106, 91, 77, 44. Anal ($C_{11}H_{13}NO_3$) C (calcd 63.76, found 65.0), H, N.

Preparation of 6,8-dimethyl-4-hydroxycarbostyryl - (8) was by cyclization of 7 (PPA, 145°, 4 hr); recrystallized (DMF); mp 355° dec (lit[3b] 360°).

3,3-Dichloro-6,8-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (9). — A reluxing solution of 8 (12:2:3 dioxane-H_2O-conc HCl) was treated dropwise with 600 ml of 30% H_2O_2 at a rate to maintain the exothermic reaction at 90-95°; 9 precipitated. After 30 min (80-85°), cooling and diluting (ice-H_2O), 9 was filtered, washed (H_2O) and dried (100°, 20 hr); yellow, mp 217-218° dec (lit[3b] 215°); 61% from 7; recryst (THF-hexane), mp 222-223° dec; mass spectrum, m/e 257 (M^+ base peak), 223, 189, 174, 158, 148, 130, 119, 104, 103, 92, 77. Anal. ($C_{11}H_9Cl_2NO_2$) C, H, N.

3,3-Dimethoxy-6,8-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (10). — Addition of a solution of 40 g of Na in MeOH (600 ml) to 9 (202 g in MeOH, 500 ml, exothermic reaction) refluxing (30 min), quenching (ice-5% HCl), filtration, and washing (H_2O), gave 10; recryst (MeOH, yellow), mp 206-208°; nmr ($CDCl_3$), δ 2.10 (s,3), 2.22 (s,3), 3.47 (s,6), 5.32 (s,1), 6.37 (s,2), 7.08 (s, broad, 1), 7.72 (s,1). Anal. ($C_{13}H_{15}NO_4$) C, H, N.

Diethoxy Analog of 10:- prepared from 9 by NaOEt; mp 191-192° dec. Anal. ($C_{15}H_{19}NO_4$) C, H, N.

2-Amino-3,5-dimethylphenylglyoxal Dimethylacetal (11). — A suspension of 10 in 1.15 l. of 6% aq NaOH was refluxed (1.25 hr), cooled (10°), saturated with NaCl, and extracted portionwise with 1.6 l. of Et_2O, giving 11 (50% from dimethylaniline); bp 127-128°/0.23 mm., Nmr ($CDCl_3$), δ 210 (s, 3), 2.22 (s, 3), 3.47 (s, 6), 5.32 (s, 1), 6.27 (s, broad, 2), 7.08 (s, 1), 7.32 (s, 1). Anal. ($C_{12}H_{17}NO_3$) C, H, N.

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5,7-Dimethyl-9-(dimethoxymethyl)-2,3-dihydro-1H-cyclopenta[b]quinoline (12).[cf 3c] — A solution of Na (2.5 g, EtOH), 11 (29.3 g) and cyclopentanone (15 g) was refluxed (17 hr) and quenched (saturated NaCl). Et_2O extraction, evaporation, and crystallizations (hexane) gave 12 (25.1 g, 70%, yellow), mp 78-80°. Anal. ($C_{17}H_{21}NO_2$) C, H, N.

3-(4-Chlorophenyl)-2-cyclopentenone (38), prepared (21%) like the phenyl analog[13]; sublimed (75°/0.3 mm), mp 96-98°; mass spectrum, m/e 192 (M^+), 157, 149, 136, 129 (base peak), 128, 127; nmr ($CDCl_3$); δ 2.60 (m,2), 3.25 (m,2), 6.59 (m,1), 7.55 (m,4). Anal. ($C_{11}H_9ClO$) C, H. Attempted condensation with 11 was unsuccessful.

3-(4-Chlorobenzylidene)-5,7-dimethyl-2,3-dihydro-1H-cyclopenta-[b]quinoline-9-aldehyde (13).[cf 3e] — A mixture of 12 (7.89 g), pClPhCHO (4.26 g), dry NaOAc (2.51 g), Na_2CO_3 (10.6 g) and Ac_2O (300 ml), was refluxed (17 hr), cooled, and hydrolized (15% NaOH). The precipitate was washed (H_2O, Et_2O, 13-acetal, 9.76 g). A mixture of an aliquot (5.67 g), $CHCl_3$ (250 ml) and 5% HCl (50 ml) was stirred (1 hr) [1:4 H_2O-THF dissolves 12 and may be preferable.] Evapn of the $CHCl_3$ and Et_2O extracts gave 13 (5.45 g, 54% from 12), mp 233-235 dec; recrystallized (THF), mp 237-239° dec; mass spectrum, m/e 347 (M^+, base peak), 346, 319, 318, 312. Anal. ($C_{22}H_{28}ClNO$) C, H, N.

3-(4-Chlorobenzylidene)-5,7-dimethyl-2,3-dihydro-1H-cyclopenta-[b]quinoline-9-ethylene Oxide (14).[cf 4] — To a mixture of THF (100 ml) and NaH (5.24 g of 54% mineral oil dispersion in DMSO, 100 ml, heated, 70°) was added THF (cooling to -5°), Me_3SI (25 g in DMSO, 175 ml, over 3-5 min, ±5°), then THF (50 ml) and 13 [9 g suspended in THF (150 ml)] over 2-3 min (-5°). Stirring, 15 min at -5° and 1.25 hr at room temperature, quenching (H_2O and saturated NaCl), extraction (Et_2O, and 2:1 Et_2O-THF), and crystallization (Et_2O), gave 14 (4.57 g, 49%), mp. 203-206° dec, recrystallized (Et_2O), yellow, mp 205-207° dec; mass spectrum, 361 (M^+, base peak), 345, 344, 343, 332, 318, 297, 296. Anal. ($C_{23}H_{20}ClNO$) C, H, N.

3-(4-Chlorobenzylidene)-5,7-dimethyl-2,3-dihydro-1H-cyclopenta-[b]quinoline-9-(α-di-n-butylaminomethyl)methanol (2). — A suspension of 14 (3.32 g) in Bu_2NH (7.5 g) was heated (under N_2, 145-150°, 9 hr, with disappearance of 14 monitored by tlc (silica gel G, Et_2O-hexane). Removal of excess Bu_2NH (55°/3 mm) and crystallization (Et_2O-THF) gave 3.63 g; recrystallized, yellow, mp 153-155° dec; uv (EtOH), nm (ε x 10^{-3}): 235 sh (1.79), 294 (28.3), 299 (29.8), 350 sh (17.5), 364 (25.2), 381 (25.2). Anal. ($C_{31}H_{39}ClN_2O$) C, H, N.

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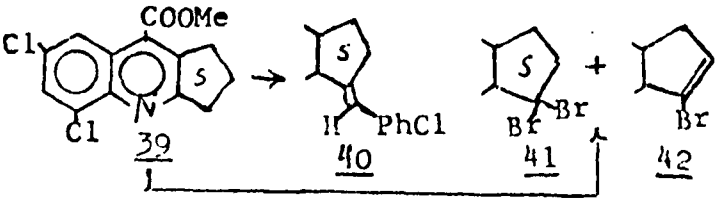
2,6,8-Trimethylquinoline-4-aldehyde Dimethyl Acetal 15.[cf3] — A soln of 11[3] (10.7 g) and Me_2CO (3 g) in abs EtOH (30 ml) was added rapidly to a 30 ml EtOH soln of Na (0.85 g). Refluxing (18 hr), quenching (aq NaCl), Et_2O extrn, vac evapn and chromatography (Florisil, 300 g, elution by hex and 9:1, 3:1 and 2:1 hex-Et_2O), gave 15, 11.29 g, (96%), tlc, single spot (silica gel-G, eluent 4:1 hex-Et_2O), bp 125-125.5°/0.33 mm, colorless; nmr ($CDCl_3$) δ 2.5 (3H,s), 2.8(3H,s), 2.8(3H,s), 3.38(6H,s) 5.9 (1H,s), 7.44(1H, broad s), 7.57(1H,s), 7.86(1H, broad s) Anal. ($C_{15}H_{19}NO_2$) C, H, N.

2-(4-Chlorostyryl)-6,8-dimethylquinoline-4-aldehyde (16).[cf3] - A mixture of 15 (12.7g), p-ClPhCHO (7.9g), anhyd NaOAc (9.8g), anhyd Na_2CO_3 (14g), and Ac_2O (300ml), was refluxed (18 hr) and quenched (ice-H_2O-KOH-NaCl). 16-Acetal was isolated by repeated extrn (THF) and hydrolyzed (THF-H_2O-conc HCl, 300/150/25 ml, brief reflux). 16 was extrd (THF, Et_2O) and recryst (Et_2O-hex); 7.51g (50%); recryst, yellow, mp 167-169°; ir (KBr): 1700 cm^{-1}; nmr ($CDCl_3$), δ 2.50 (3H, s), 2.78 (3H, s), 7.12-7.65 (7H, m), 7.81 (1H, s), 8.47 (1H, broad s), 10.14 (1H, s). Anal. ($C_{20}H_{16}ClNO$) C,H,N.

2-(4-Chlorostyryl)-6,8-dimethylquinoline-4-ethylene Oxide (17).[4] - Prepared like 14; recryst (Et_2O), yellow, mp 141-142°. Anal. ($C_{21}H_{18}ClNO$), C,H,N. Reaction with $NHBu_2$ (140-145°, 9 hr, under N_2) was shown to be incomplete (by H. R. Munson) by tlc; mass spectrum, m/e 464 (3), 142 (CH_2NHBu_2).

2-(4-Chlorostyryl)-6,8-dimethylquinoline-4-(α-di-n-butylaminomethyl) methanol·HCl (3). - To NaH (1.8g, Et_2O-Washed) in DMSO (10 ml, 70°, 1 hr), was added THF (50 ml), cooling to and maintaining below 0°. TMSI (8g in DMSO(50 ml) was added slowly, then 16 (2.3g in THF), stirring (25°, 3 hr). After pouring into H_2O, extrn (Et_2O), drying (Na_2SO_4), evapn, addn of $NHBu_2$ (10 ml) to the residue (17), and heating (160°, under N_2, 18 hr), and vac evapn of excess $NHBu_2$, the product was chromatographed (silica gel, EtOAc-C_6H_6). 3·HCl was pptd by Et_2O-HCl: 1.5g (40%), mp 125-130° (decomp, requires vac drying). Anal. $C_{29}H_{38}Cl_2N_2O$(C,H,N). Nmr, CI mass spectra: compatible.

Derivatives of 5,7-Dichloro-2,3-dihydro-1H-cyclopenta[b]quinoline-9-carboxylic Methyl Ester 39-40[1] as intermediates for synthesis of antimalarials



3-(4-Chlorobenzylidine)5,7-dichloro-2,3-dihydrocyclopenta[b]quinoline-9-carboxylic Methyl Ester (40). — A mixture of 39 (29.6 g), 4-ClPhCHO (1.47 g), dry NaOAc (9 g) and Ac_2O (200 ml), was refluxed (18 hr) and quenched (ice-H_2O). Stirring (1.5 hr), basification (50% KOH),

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washing the precipitate (H_2O, and Et_2O) and crystallization ($CHCl_3$), gave 39, 25 g (88%); recrystallized ($CHCl_3$), yellow needles, mp 280-283° dec; mass spectrum, m/e 417 (M^+, base peak), 416, 402, 382, 358, 322, 298, 251, 161, 149, 144, 143, 126, 125. Anal. ($C_{21}H_{14}Cl_3NO_2$) C, H, N. A similar condensation with the acid of 39 was unsuccessful. The acid of 40. A refluxing suspension of ester 40 (22 g) in 400 ml of THF (400 ml) to which was added 7.5 g of KOH (in 200 ml of H_2O), after 20 hr, was quenched (ice-H_2O); and acidification (concd HCl), gave 20.9 g (98%), recrystd (H_2O-THF), yellow, mp 297-300° dec. Anal. ($C_{20}H_{12}Cl_3NO_2$) C, H, N.

Bromination of 39. A stirred suspension (12 g) and NaOAc (13.5 g) in AcOH (100 ml, 50-70°) was treated dropwise (3 hr) with Br_2 (13 g in 100 ml of AcOH), and (after 1 hr) was quenched (ice-H_2O), giving 10.5 g of 41-42 mixture (separated by chromatographing, fluorisil, elution with hexane and 9:1 hexane-C_6H_6).

3,3-Dibromo-5,7-dichloro-2,3-dihydro-1H-cyclopenta[b]quinoline-9-carboxylic Methyl Ester (41); recrystallized (charcoal, Et_2O), mp 166-168°. Anal. ($C_{14}H_9Br_2Cl_2NO_2$) C, H, N.

3-Bromo-5,7-dichloro-1H-cyclopenta[b]quinoline-9-carboxylic Acid Methyl Ester (42); insoluble in Et_2O; charcoaled (C_6H_6, reflux); 0.29 g. recrystallized (C_6H_6), mp 165-170°. Anal. ($C_{14}H_8BrCl_2NO_2$) C, H, N.

New Compounds by B. B. Corson, J. Riedmaier, J. Pociask and H. Koppel, (mp) analyzed (C,H,N,Br,Cl within ± 0.4%). 5 - 19, $C_{15}H_{15}NO_2$, 21(124-125°)$C_{16}H_{17}NO$, 22·HBr(195-196°dec.)$C_{16}H_{17}Br_2NO$, 23(140-141°) $C_{16}H_{17}NO$, 24(67.5-69°)$C_{24}H_{38}N_2O$, 25(192.5-193.5°)$C_{20}H_{18}N_2O$, 26 (221-225°)$C_{20}H_{26}N_2O$, 27 from 26 by p-ClPhCHO, 26/1 ml Py/pip, 80-95°, 8 hr (148-150°)$C_{27}H_{29}ClN_2O$;nmr($CDCl_3$)δ7.5-7.8(m,6H), 6.16, 5.70 (dd 1H, carbinol C-H, 2 diastereomers), 4.82(bs,1H), 2.78, 2.47(s, 3H each, CH_3), 27.2HCl(dried, 1mm, 2 hr, 22°)$C_{27}H_{29}ClN_2O·2HCl$(Cl, Cl). 2 from 24 by p-ClPhCHO, 50/2ml Py/pip, 100°(149.5-153°) $C_{31}H_{39}ClN_2O$(yield 3%, yellow)(anal, nmr compatible).

5,7-Dimethyl-4-(p-chlorobenzilidine-1,2,3,4-tetrahydroacridine-9-(α-N-piperidinomethyl)methanol (37), by R. G. Bass and R. R. Hirjibedin[11] (Scheme IV). New compounds (mp) analyzed (C,H,N±0.4).- 28(74-75°)$C_{18}H_{23}NO_2$. 29(110-111°, yellow)$C_{16}H_{17}NO$. 30(175-177°) $C_{23}H_{20}ClNO$. 31(93-95°)$C_{17}H_{19}NO$. 32(171-172°)$C_{24}H_{22}ClNO$. 34(198-200°) $C_{21}H_{22}N_2O$. 35(222-223°)$C_{28}H_{25}ClN_2O$. 36(158-160°)$C_{25}N_{26}Cl_2NO_2$. 37 (207°)$C_{29}H_{33}ClN_2O$. Ir, nmr and mass spectra were compatible with 28-37,[11] but 33(mp 84-86°) did not analyze correctly.

Acknowledgements. A test sample of 2-(p-chlorostyryl) amino-alcohol 3 was prepared by D. A. Shamblee at Robins Co., Richmond, Va., working under S. J. Gillespie, Virginia Institute for Scientific Research, Richmond, Va. Work done independently is here reported (with permission[8,11]) on: synthesis of 27 and a second synthesis of 2 by B. B. Corson, J. Riedmaier, J. Pociask and H. C. Koppel, Preparations Lab., Aldrich Chemical Co., Milwaukee, Wis.; and synthesis of 37 by R. G. Bass and R. R. Hirjibehedin, Virginia

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V. Part 7. Footnotes and References

#Contribution No. of the Army Research Program on Malaria. This work was supported (a) in large part by U. S. Army Medical Research and Development Command, Office of the Surgeon General, Contract No. DA-48-193-MD-2955, R. E. Lutz, Responsible Investigator; and (b) in smaller parts by grants to R.E.L. from: (c) National Science Foundation (8631); and (d) A. H. Robins Co., Richmond, Va. (e) Antimalarial test data supplied by Walter Reed Army Institute for Research. (f) Laboratory work terminated 1970 by retirement of R.E.L. The test sample of 3 was made by D. A. Shamblee at Robins Co., directed by S. J. Gillespie, Virginia Institute for Scientific Research, 1974.

&Postdoctoral Research Associate. *To whom inquiries may be directed.

Instruments: Thomas-Hoover apparatus for mp; ir, Perkin-Elmer 337; nmr, Hitachi-P. E. R-20; mass spectrum, Hitachi P. E. RMU 6E. Microanal.: Gailbraith Lab., Inc., correct ±0.4%.

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Analytical Data on new Compounds

"Antimalarials. 11."
J. M. Sanders and R. E. Lutz

Compd No.	formula	Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
2	$C_{31}H_{39}ClN_2O$	75.82	8.00	5.70	75.64	8.14	5.64
		Cl, 7.22				7.07	
7	$C_{11}H_{13}NO_3$	63.76	6.32	6.76	64.98	6.41	6.75
9	$C_{11}H_9Cl_2NO_2$	51.19	3.51	5.43	51.35	3.66	5.29
10	$C_{13}H_{15}NO_4$	62.64	6.07	5.62	62.84	6.14	5.40
10-diOEt analog	$C_{15}H_{19}NO_4$	64.96	6.90	5.05	64.77	6.95	4.96
11	$C_{12}H_{17}NO_3$	64.55	7.68	6.27	64.28	7.70	6.02
12	$C_{17}H_{21}NO_2$	75.24	7.80	5.16	75.50	7.92	5.17
13	$C_{22}H_{18}ClNO$	75.97	5.21	4.03	75.82	5.22	3.80
14	$C_{23}H_{20}ClNO$	76.34	5.57	3.87	76.28	5.60	3.65
16	$C_{21}H_{14}Cl_3NO_2$	60.24	3.37	3.34	60.24	3.26	3.28
16-acid	$C_{20}H_{12}Cl_3NO_2$	59.36	2.99	3.46	59.52	3.02	3.31
17	$C_{14}H_9Br_2Cl_2NO_2$	37.04	2.00	3.09	37.21	1.97	3.08
18	$C_{14}H_8BrCl_2NO_2$	45.08	2.16	3.76	45.13	2.15	3.78
38	$C_{11}H_9ClO$	68.58	4.71	---	68.37	4.87	---
19	$C_{15}H_{19}NO_2$	73.44	7.80	5.71	73.46	7.85	5.86
20	$C_{20}H_{16}ClNO$	74.65	5.01	4.35	74.63	5.22	4.17
21	$C_{21}H_{18}ClNO$	75.11	5.40	4.17	71.11	5.31	4.01
by Corson, Riedmaier, Pociask, Koppel, Compounds[10] of Scheme IV.							
19	$C_{15}H_{15}NO_2$			5.81			5.75
21	$C_{16}H_{17}NO$:	80.3	7.16	5.85	80.38	7.13	5.89
22	$C_{16}H_{17}Br_2NO$	48.15	4.46	3.51	3.83	3.51	3.85
			(Br, 40.05			39.68)	
23	$C_{16}H_{17}NO$	80.3	7.16	5.85	79.90	7.43	5.45
24	$C_{24}H_{36}N_2O$	78.21	9.85	7.60	78.29	9.86	7.63
25	$C_{20}H_{18}N_2O$	79.44	6.00	9.27	80.00	6.13	9.26
26	$C_{29}H_{26}N_2O$			9.03			8.86
27	$C_{27}H_{29}ClN_2O$	74.89	6.75	6.47	74.99	6.65	6.45
27·2HCl	$C_{27}H_{29}ClN_2O\cdot 2HCl$	Cl, Cl: 7.01, 14.02;				6.05, 14.7	
By Bass and Mirjibedin, Compounds[11] of Scheme V.							
28	$C_{18}H_{23}NO_2$	75.77	8.12	4.91	75.93	8.17	4.99
29	$C_{16}H_{17}NO$	80.30	7.16	5.85	80.09	7.24	5.74
30	$C_{23}H_{20}ClNO$	76.34	5.57	3.87	76.07	5.61	3.71
31	$C_{17}H_{19}NO$	80.60	7.56	5.53	80.29	7.46	5.62
32	$C_{24}H_{22}ClNO$	76.69	5.90	3.73	76.53	5.95	3.62
34	$C_{21}H_{20}N_2O$	79.21	6.96	8.80	78.96	7.05	8.73
35	$C_{28}H_{25}ClN_2O$	76.26	5.71	6.35	76.23	5.79	6.36
36	$C_{29}H_{26}NClO_2$	75.61	6.42	3.43	73.34	6.35	3.32
37	$C_{20}H_{22}ClON_2$	75.55	7.21	6.08	75.45	7.20	5.86

VII. List of Publications On Work Under This Contract.

Antimalarials. Cf. Annual Reports by R.E.L., 1967, 1968, 1969.

1. Pyridyl Ketones by Addition of Pyridyllithium to Carboxylic Acids. A New Synthesis of α-(2-Piperidyl)-2-aryl-4-quinolinemethanols.
J. HETEROCYCLIC CHEMISTRY, 4, 459 (1967). *D. W. Boykin, A. R. Patel, R. E. Lutz, and A. Burger.*

2. **α-(2-Piperidyl)- and α-(2-Pyridyl)-2-trifluoromethyl-4-quinolinemethanols.**
ROGER M. PINDER AND ALFRED BURGER. Journal of Medicinal Chemistry, 11, 267 (1968).

3. **Benzothiazole Amino Alcohols.** ALFRED BURGER[1b] AND S. N. SAWHNEY.
Journal of Medicinal Chemistry, 11, 270 (1968).

4. **New Synthesis of α-(2-Pyridyl)- and α-(2-Piperidyl)-2-aryl-4-quinolinemethanols**
D. W. BOYKIN, JR., A. R. PATEL, AND R. E. LUTZ. Journal of Medicinal Chemistry, 11, 273 (1968).

5. **α-Dibutylaminomethyl- and α-(2-Piperidyl)-3-quinolinemethanols.**
CYRUS J. OHNMACHT, JR., FREDDY DAVIS, AND ROBERT E. LUTZ. J. Medicinal Chemistry, 14, 17 (1971).

6. **Some New α-Alkylaminomethyl-4-quinolinemethanols** *J. Medicinal Chemistry, 1971, 14,* [illegible].
A. R PATEL, C. J. OHNMACHT, D. P. CLIFFORD, A. S. CROSBY, AND R. E. LUTZ.

7. **Bis(trifluoromethyl)-α-(2-piperidyl)-4-quinolinemethanols.**
Journal of Medicinal Chemistry, 14, 926 (1971). C. J. OHNMACHT, A. R. PATEL, AND R. E. LUTZ

8. **2,3-Trimethylene-4-quinoline Amino Alcohols. 5,7-Dichloro-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-(α-di-*n*-butylaminomethyl)methanol.**
J. M. SANDERS, D. P. CLIFFORD, AND R. E. LUTZ. Journal of Medicinal Chemistry, 14, 1126, (1971).

9. **α-(2-Piperidyl)-4-quinolinemethanols Carrying 2-Aroxy- and 2-(*p*-Chloroanilino) Groups.**
Charles R. Wetzel, James R. Shanklin, Jr., and Robert E. Lutz.
Journal of Medicinal Chemistry, 16, 528 (1973).

10. 3-Substituted-2-aryl-4-quinoline Aminoalcohols.
H. R. Munson, Jr., R. E. Johnson, J. M. Sanders, C. J. Ohnmacht and R. E. Lutz, Manuscript (p. 37), to be submitted to J. Med. Chem.

11. Syntheses of 2-Vinylogs of Substituted 2-Aryl-4-quinoline Amino-alcohols. 3-(4-Chlorobenzylidine)-5,7-dimethyl-1,2-dihydro-1H-cyclopenta[b]quinoline-9-(α-di-n-butyl-aminomethyl)-methanol.
J. M. Sanders and R. E. Lutz, Manuscript (p. 54), to be submitted to J. Med. Chem.

12. Quinoline Syntheses by Reaction of Hydrazoic Acid with α,β-Disubstituted *cis*-Chalcones.
JOURNAL OF HETEROCYCLIC CHEMISTRY 7, 1051 (1970).
Robert E. Pratt, William J. Welstead, Jr. and Robert E. Lutz.

(This work was not financially supported by WRAIR, but was of interest and possibly applicable in V. Part 6.)

VII. List of Publications by R. E. Lutz on World War II Research Under the Committee on Medical Research. Aminoalcohols as Potential Antimalarials.

1. **Antimalarials.**[1] **α-Alkyl and Dialkylaminomethyl-2-phenyl-4-quinolinemethanols**

By Robert E. Lutz, Philip S. Bailey,[2a] Marion T. Clark,[2b] John F. Codington,[2c] Adolph J. Deinet,[2d] James A. Freek, Grant H. Harnest,[2d] Norman H. Leake,[2e] Tellis A. Martin, Russell J. Rowlett, Jr.,[2c] Jason M. Salsbury,[2f] Newton H. Shearer, Jr.,[2c] J. Doyle Smith[2b] and James W. Wilson, III[2d]

American Chemical Society, 68, 1813 (1946)

2. **Antimalarials. 6- and 7-Chloro-α-(dialkylaminomethyl)-4-quinolinemethanols**

American Chemical Society, 69, 1260 (1947).

By Robert E. Lutz, John F. Codington[2a] and Norman H. Leake[2b]

3. **ANTIMALARIALS. α-PHENYL-β-DIALKYLAMINO ALCOHOLS**[1]

Journal of Organic Chemistry Vol. 12, No. 5, September, 1947

ROBERT E. LUTZ, RUFUS K. ALLISON,[2a] GILBERT ASHBURN, PHILIP S. BAILEY,[2b, 3] MARION T. CLARK,[2c] JOHN F. CODINGTON,[2d] ADOLF J. DEINET,[2e] JAMES A. FREEK, ROBERT H. JORDAN, NORMAN H. LEAKE,[2f, 3] TELLIS A. MARTIN, KENT C. NICODEMUS, RUSSELL J. ROWLETT, JR.,[2g, 3] NEWTON H. SHEARER, JR.,[2b] J. DOYLE SMITH,[2i] AND JAMES W. WILSON, III[2j, 3]

4. **Antimalarials. 2,5-Diphenyl-3-furyl Amino Ketones and Alcohols**

American Chemical Society, 70, 1359 (1948).

By Robert E. Lutz and Russell J. Rowlett, Jr.[2]

5. **ANTIMALARIALS.**[1] **ALIPHATIC AMINO KETONES AND ALCOHOLS**

Journal of Organic Chemistry Vol. 12, No. 6, November, 1947

ROBERT E. LUTZ AND JAMES W. WILSON, III[2]

6. **ANTIMALARIALS.**[1] **SOME NEW LONG-CHAIN ALIPHATIC DI-(AMINO ALCOHOLS)**

Journal of Organic Chemistry Vol. 12, No. 6, November, 1947

JAMES W. WILSON, III,[2] ROBERT E. LUTZ, AND ROBERT H. JORDAN

7. **ANTIMALARIALS.**[1] **SOME PIPERAZINE DERIVATIVES**

Journal of Organic Chemistry Vol. 11, No. 6, November, 1947

ROBERT E. LUTZ AND NEWTON H. SHEARER[2]

8. **Secondary and Tertiary Amino Ketones and Alcohols Derived from Desoxybenzoin and 1,2-Diphenylethanol.**[1] **Ring-Chain Tautomerism of the α-(β-Hydroxyethylamino) Ketones**[2]

Journal of the American Chemical Society, 70, 2015 (1948).

By Robert E. Lutz, James A. Freek[3a] and Robert S. Murphey[3b]

9. **Substituted-Amino Ketones and Alcohols Related to 4,4′-Dichlorobenzoin**

American Chemical Society, 71, 478 (1949).

By Robert E. Lutz and Robert S. Murphey[2]

10. **Ring-Chain Tautomerism of α-(Ethylethanolamino)-acetophenone**

Journal of the American Chemical Society, 71, 990 (1949).

ByRobert E. Lutz and Robert H. Jordan[2]

11. **The Preparation of 4-Ethyl-2-methoxy-2-phenyl-morpholine**

Journal of the American Chemical Society, 72, 1409 (1950).

By Robert H. Jordan[1] and Robert E. Lutz

12. **Factors Interfering with the Oppenauer Oxidation of Amino Alcohols**

Journal of the American Chemical Society, 72, 1085 (1950).

By Robert E. Lutz, Robert H. Jordan,[2a] and William L. Truett[2b,c]

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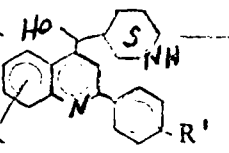
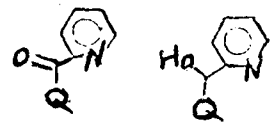
VIII. List of New Compounds# Submitted to WRAIR.

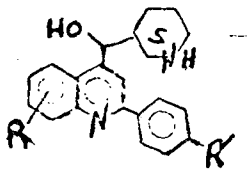
A. 76 New Aminoalcohols for Antimalarial test and some of their 2-pyridyl ketones and alcohols.

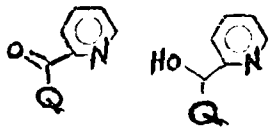
List No.	R	R'	REL No.	AB No.	WRAIR No.	Page No. (Refs p67)
1	6-Me	H	869	746	7934	9^4
2	8-Me	H	854	719	7552B	↓
3	8-CF_3	H	851	716	62175A	↓
4 → 5	6-Me	H	819	674	54406	8^4
5	6-Me	H	820	675	54407	↓
6	8-Me	H	865	742	73897	↓
7	8-Me	H	853	718	62177	↓
8	6,8-Me_2	H	866	743	73962	↓
9	6,8-Me_2	H	852	717	62176	↓
10	8-CF_3	H	867	744	73896	↓
11	8-CF_3	H	850	715	62174	↓
12 → 18	6-Me	Me	842	707	62189A	9^4
13	8-Me	Me	857	734	73871	↓
14	6,8-Me_2	Me	844	709	62187	↓
15	Q-CHOHCH$_2$NBu$_2$·HCl	Me	870	760	75261	15^6
16	Q-CHOHCH$_2$NEt$_2$·HCl	Me	871		79326	15^6
17	6-F	Me	922			15^6
18	8-CF_3	Me	845	710	62186	9^4
19 → 26	6-Me	Me	807	662	54424	8^4
20	6-Me	Me	809	664	54426	↓
21	8-Me	Me	856	733	73901	↓
22	8-Me	Me	858	735	73899	↓
23	6,8-Me_2	Me	817	672	54401	↓
24	6,8-Me_2	Me	818	673	54405	↓
25	6-OMe	Me	821	676	54408	↓
26	6-OMe	Me	822	677	54409	↓

#For the first year of this project Dr. Alfred Burger and REL divided personnel and research supervision while Dr. Burger administered submission of samples from both groups to WRAIR under AB numbers (REL extended his personal file for his group using REL numbers). After REL became sole Principal Investigator, compounds were then submitted under REL numbers. Thus, where two numbers are given, it is for an REL compound which had been submitted during the first year to WRAIR and indexed there under AB numbers.









		R	R'				
27	→	6-F	Me	892		45112	8^4
28		8-CF_3	Me	831	686	54418	
29		8-CF_3	Me	832	687	54419	
30	→	8-Me	Me	857	740	73891	
31		8-Me	Cl	855	732	73892	9^4
32		6,8-Me_2	Cl	868	745	73898	
33		8-CF_3	Cl	849	714	62182	
34	→	6-Me	Cl	808	663	54425	8^4
35		6-Me	Cl	810	665	54427	
36		8-Me	Cl	864	741	73895	
37	→	6,8-Me_2	Cl	829	684	54416	
38		6,8-Me_2	Cl	830	685	54417	
39		8-CF_3	Cl	827	682	54414	
40		8-CF_3	Cl	828	683	54415	
41		8-CF_3	F		688	54420	
42		8-CF_3	F		684	54421	
43	→	8-Me	F	861	738	73893	9^4
44		6,8-Me_2	F	848	713	62183	
45		6-Me	OMe	843	708	62188	
46		6,8-Me_2	OMe	846	711	62185	
47		8-CF_3	OMe	847	712	62184	
48	→	6-Me	F	813	668	54403	8^4
49		6-Me	F	814	669	54400	
50		8-Me	F	862	739	73894	
51		6,8-Me_2	F	823	678	54401	
52		6,8-Me_2	F	824	679	54411	
53		8-CF_3	F	834	689		
54		8-CF_3	F	833	688		
55		6-Me	OMe	815	670	54401	
56		6-Me	OMe	816	671	54402	
57		8-Me	OMe	860	737	73903	
58		8-Me	OMe	859	736	73900	
59		6,8-Me_2	OMe	825	680	54412	
60		6,8-Me_2	OMe	826	681	54413	
61		8-CF_3	OMe	835	690	54422	
62		8-CF_3	OMe	836	691	54423	

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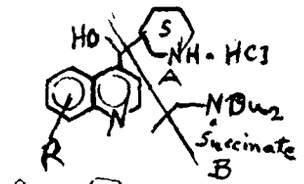
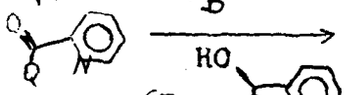
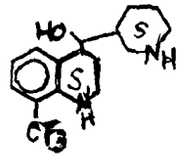
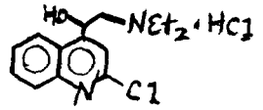
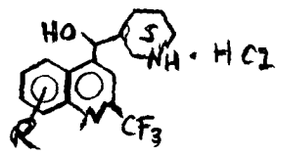
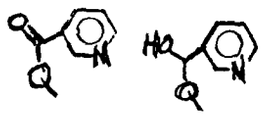
			R			
63		B	7-CF_3	957	144238	15[6]
64		A	8-CF_3	943	121475	
65			7-CF_3	976	159960	
66			8-CF_3	923	113250	
67			8-CF_3	925	113252	
68				944	121476	
69				935	115228	36[9]
70			H		725 69053	19[2]
71			6-Me		750 75435	
72			8-Me		721 73879	
73			6,8-Me_2		731 73872	
74			6-Cl		748 75437	
75			8-Cl			
76			6F	936	117108	
77			6,8-Cl_2			
78			8-F	937	117107	
79			6-OMe		727 [illegible]	
80			6-CF_3	972	157309	22[7]
81			7-CF_3	969	155066	
82			8-CF_3	956	142490	
83			6-OMe,8-CF_3	974	159314	



84	H		724	69055	19[3]
85	6-Me		749	75436	
86	8-Me		728	73883	
87	6,8-Me_2		730	73887	
88	6-Cl		747	75438	
89	6-F	906		109935	15[1]
90	6-F	904		109936	
91	6-OMe		726	69049	19[2]
92	6-OMe,8-CF_3	977		159933	22[7]

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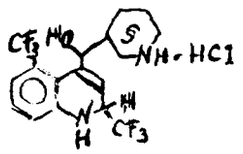
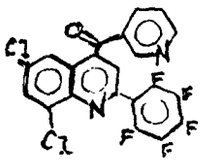
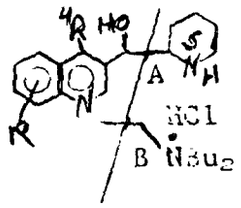
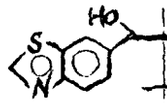
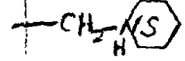
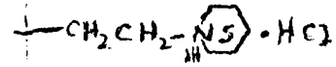
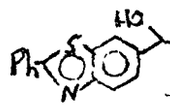
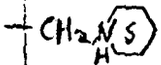
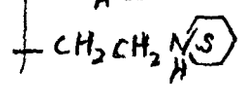
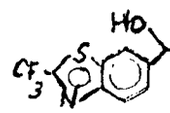
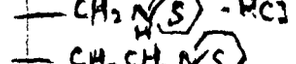
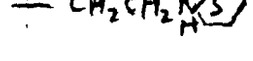
93					975	159933	21^7
94					979	159935	16
			R	^{4}R			
95		A	6,8-Me_2	H	953	140090	23^5
96		B	6,8-Me_2	4-Cl	947	133090	
97		B	6,8-Cl_2	H	954	142492	
98		B·2HCl	7-Cl	4-Cl	948	134482	
99		B	8-CF_3	H	955	142491	
100			8-CF_3	4-Cl	951	136557	
101			6,8-Cl_2	4-Cl	946	125432	
102			8-phenyl	4-Cl	950	136230	
103		$CH_2NEt_2 \cdot 2HBr$			721	62179	32^3
104		CH_2NBu_2 · methylene bis-3-(2-OH, naphthoate)			751	75252	
105		$CH_2CH_2NMe_2 \cdot 2HCl$			752	75253	
106		 base			720	62178	
107					753	75254	
108		CH_2NEt_2			723	62181	
109		$CH_2CH_2NMe_2$			755	75256A	
110					722	62180	
111					754	75255	
112		CH_2NEt_2 · methylene bis-3-(2-OH, naphthoate)			756	75257	
113		$CH_2CH_2NMe_2$			758	75259	
114					757	75258	
115					759	75260	

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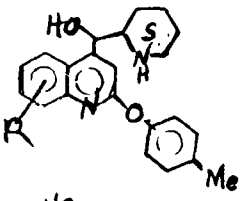
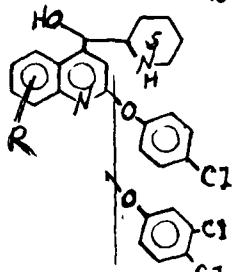
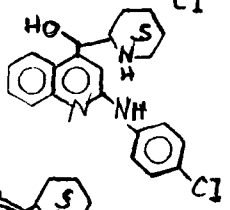
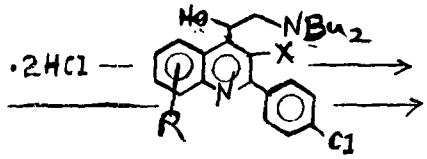
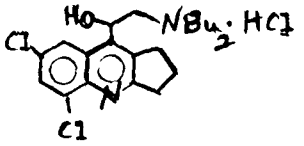
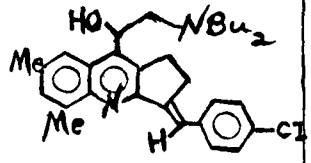
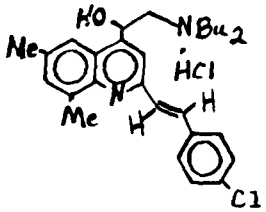
		R	X			
116		H		932	115726	36[9]
117		6-Me		933	115226	
118		6-Cl		934	115224	
119		H		940	121472	
120		$6,8\text{-Me}_2$		945	122950	
121		6-Cl		965	148987	
122		$6,8\text{-Cl}_2$		970	157308	
123		$6,8\text{-Cl}_2$		973	158284	
124		H		931	115225	
125		6-Me		930	115224	
126		$6,8\text{-Me}_2$		939	117110	
127		6-Cl		938	117109	
						
	128	H		928	115222	
	129	6-Me		929	115223	
130		H	Br	941	121473	42[10]
131		$6,8\text{-Cl}_2$	Cl	952	140089	
132		$6,8\text{-Cl}_2$	F	966	149105	
133		$6,8\text{-Me}_2$	OMe	971	157307	43[10]
134				949	135616	56[8]
135				982	160991	61[11]
136				986		62

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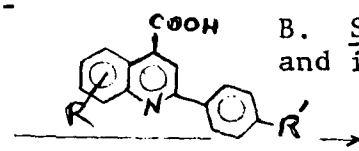
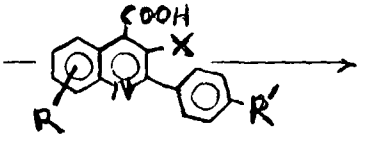
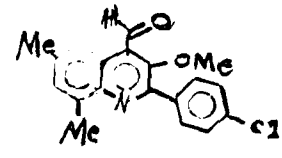
B. Supplemental List. Earlier-stage intermediates and incidental compounds



		R	R'				
1	→	6-Me	Me	841	696	54439	10^4
2	Q-COOEt	6-Me	Me	804	659	54432	↓
3	Q-COMe	6-Me	Me	806	661	54434	
4	Q-$COCH_2Br$	6-Me	Me	885		95105	
5	Q-COOH →	8-Me	Me	881		95102	
6		$6,8\text{-Me}_2$	Me	891		95111	
7		6-F	Me	886		95106	
8		6-OMe	Me	876		95097	
9		6-Me	Cl	800	655	54428	
10	QCOOEt	6-Me	Cl	801	656	54429	
11	QCOMe	6-Me	Cl	812	667	54436	↓
12	QCOOH	8-Me	Cl	883		15103	
13		$6,8\text{-Me}_2$	Cl	838	693	50482B	
14		6-F	Cl	887		95107	10^4
15		6-OMe	Cl	882		54353	
16		6-Me	F	874		95095	10^4
17	Q-COMe	6-Me	F	811	666	54435	↓
18	Q-COOH	8-Me	F	889		100925	
19		$6,8\text{-Me}_2$	F	875		95096	
20		6-F	F	894		95114	
21		6-OMe	F	884		95104	10^4
22	↓	6-Me	OMe	802	657	54430	
23	Q-COOEt	6-Me	OMe	803	658	54431	
24	Q-COMe	6-Me	OMe	805	660	54433	15^6
25	Q-$COCH_2Br$	6-Me	OMe	890		95110	↓
26	Q-COOH	8-Me	OMe	888		95108	
27	↓	$6,8\text{-Me}_2$	OMe	837	692	54437	
28	QCOMe	$6,8\text{-Me}_2$	OMe	893		95113	↓
29	Q-COOH	6-OMe	OMe	879		95099	
30		8-CF_3	H	880		95101	
31		8-CF_3	Me	877		95098	
32		8-CF_3	Cl	839	694	45852B	
33		8-CF_3	F	840	695	54438	
34	↓	8-CF_3	OMe	878		95100	



		R	X	R'			
35	→	H	Br	H	941	96685	38^{10}
36		H	Cl	H	942	1474	
37		7-Cl	Cl	Cl	959	147046	
38		$6,8\text{-Cl}_2$	Cl	Cl	958	147046	
39		$6,8\text{-Cl}_2$	F	Cl	978	15961	
40		H	NH_2	H	873	95094	



41					983	160987	↓

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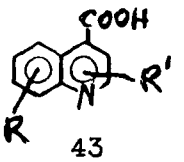
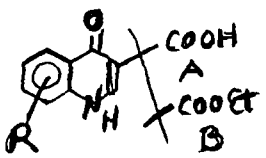
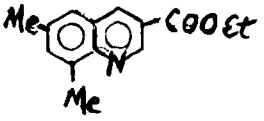
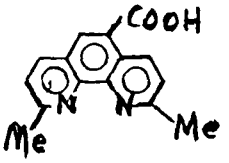
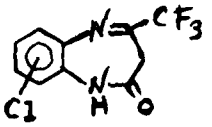
			R^{6-8}	R^{2-3}			
42			7-Br	H	913	109930	15^6
43		Q-COOEt	7-Br	H	921	109929	
44			7-Cl	H	919	061942	
45			7-Cl	2-COOH	920	109221	
46			6,8-Cl_2	Cl	927	115221	
47			7-F	H	918	109933	
48			7-CF_3	H	916	109923	
49			7-CF_3	2-COOH	915	109922	
50			8-CF_3	H	917	109920	
50A			8-CF_3	2-COOH	914		
			R				
51		A	6,8-Cl_2		963	148986	27^5
52		B	6,8-Me_2		962	50045	
53		B	6-OMe		964	67704	
54		B	8-CF_3		960	85308	
55		B	8-CF_3 (4-OH form?)		926	85308	
56		B	8-phenyl		961	148985	
57					981	159935	27^5
58					980	159934	
59			mp 183-185°		968	153180	
60			mp 258-260°		967	153179	

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Seventysix new aminoalcohols, chiefly of the 4-quinoline type, were synthesized, following older leads and in exploration of new ones, hoping to eliminate phototoxicity. However, the highly curative compound WR 30090 made during World War II by the Virginia group, despite severe phototoxicity in animals, proved highly successful as prophylactic and cure for several strains (Cont. on back)		

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19. (Continued)
2-Trifluoromethyl-4-quinolinemethanols
Bis-trifluoromethyl-4-quinolinemethanls
2-aroxy-4-quinolinemethanols
2-(N-p-chloroanilino)-4-quinolinemethanols
2,3-Trimethylene-4-quinolinemethanols
1,2-Dihydro-1H-cyclopenta[b]quinoline-9-methanol
3-(4-Chlorobenzylidine)-1,2-etc.

Note: In the above, aminoalcohols may be substituted for "methanols".

20. (Continued)

of P. falciparum in man, with phototoxicity inconsequential.

(1) Nineteen new 2-aryl-4-quinoline aminoalcchols proved highly active and curative against P. berghei but were phototoxic in animals.

(2) Ten 2-CF_3 derivatives showed moderate antimalarial activities; and four 6,8-bis-CF_3 analogs were highly curative and non-phototoxic. The 2,8-bis-CF_3 compound proved highly successful in man.

(3) Shifting the aminoalcohol chain from quinoline position-4 to 3 was ineffective in eight compounds without a 2-aryl.

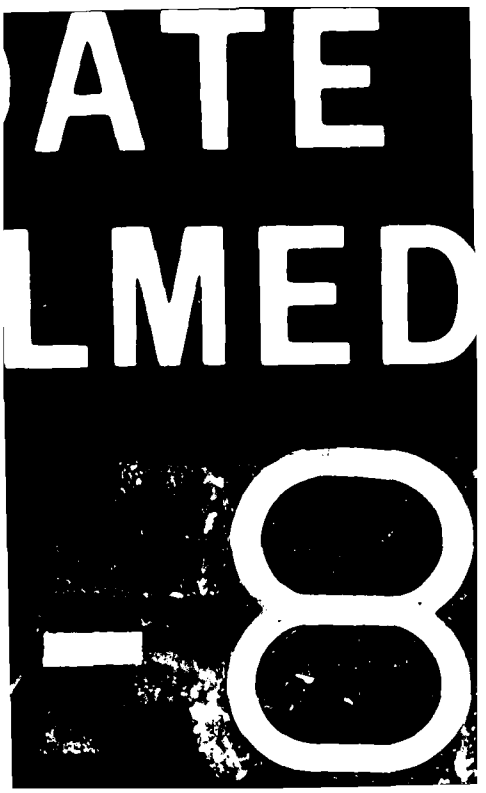
(4) Twelve 6-benzothiazole aminoalcohols proved ineffective.

(5) Twelve 4-quinoline aminoalcohols carrying 2-p-substituted-phenoxy or 2-(N-pCl-anilino), where nuclear through-conjugation is interrupted by the heteroelement, were curative but phototoxic in animals.

(6) Four 2-aryl-quinoline aminoalcohols carrying Cl, Br, F, or OMe in the 3-position (to sterically interfere with the nuclear planarity and through-conjugation), showed high curativity but were phototoxic.

(7) The 6,8-dichloro-4-quinoline aminoalcohol with a 2,3-trimethylene fused ring proved to be moderately active and non-phototoxic. The 6,8-Me_2 analog with pClPhCH= at the 2-CH_2 group, is a 2-vinylog of the 2-aryl-4-quinoline aminoalcohols, and it carries the p-chlorostyryl group at the quinoline position-2 and extruding as a part of the rigid 2,3-tricarbon fused ring. This was highly curative in spite of the relatively poor auxopharmocophoric quality of the 6,8-dimethyls. It was non-phototoxic in animals.

The supposed alpha-piperidyl analog (Corson, Aldrich Chem. Co.) made through a last step condensation of the secondary-amino alcohol with pClPhCHO, is now shown to be the oxazolidine.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